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OF

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VOLUME 55 - NUMBER 3
SEPTEMBER 1961

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1. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Eisfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

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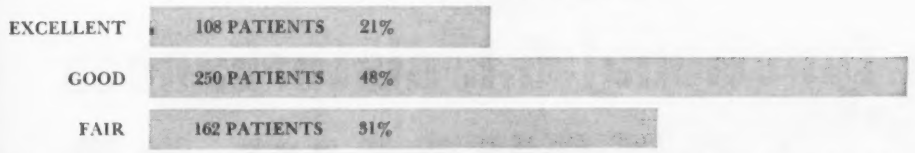
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references: (1) Crepea, S. B.: J. Allergy 31:283-285 (May-June) 1960. (2) Clinical Research Division, Mead Johnson & Company. (3) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. 35:161-169 (March 30) 1960.

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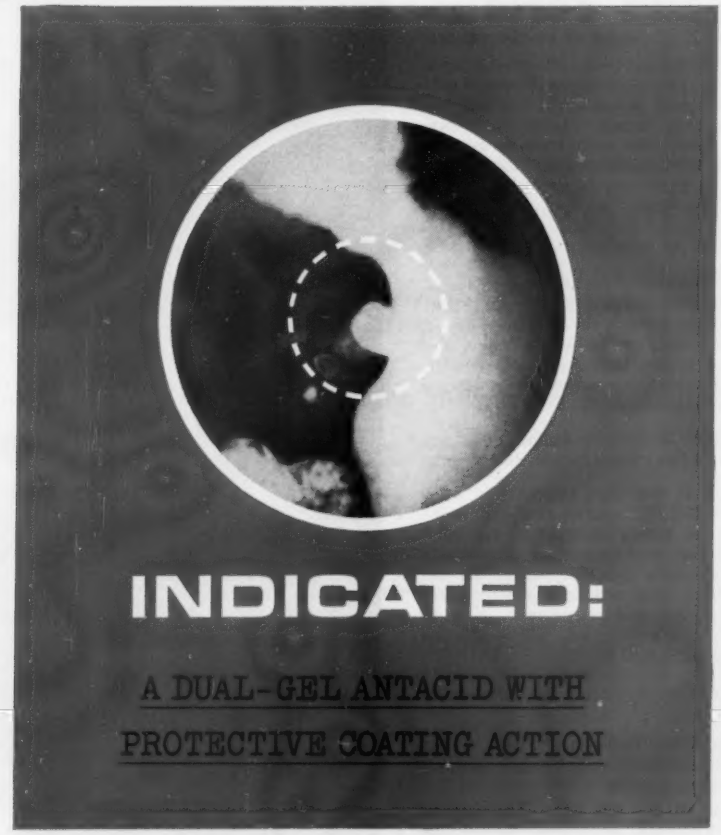
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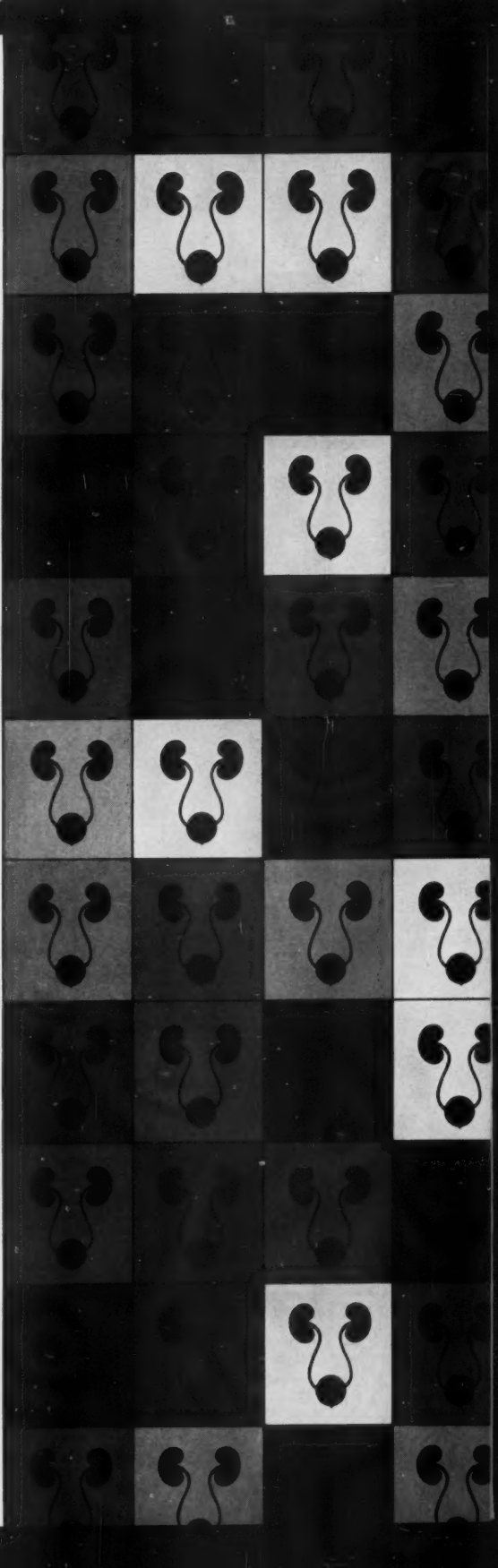
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References: 1. Bourque, J.-P., and Gauthier, G-E.: L'Union Medicale **89**:640 (May) 1960. 2. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. **56**:66 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. **68**:337 (Apr.) 1953. 4. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. **17**:320 (July) 1956.

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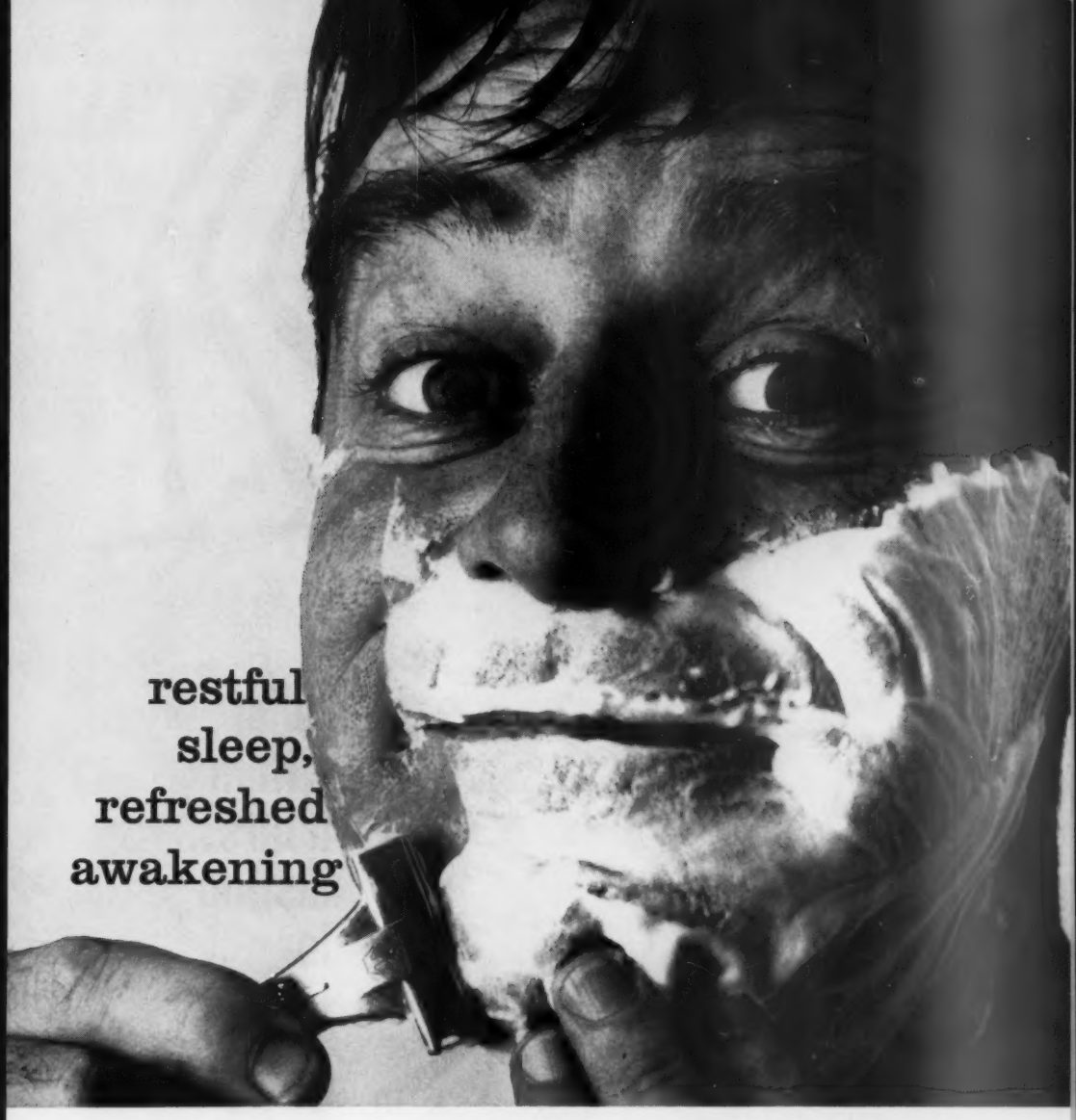
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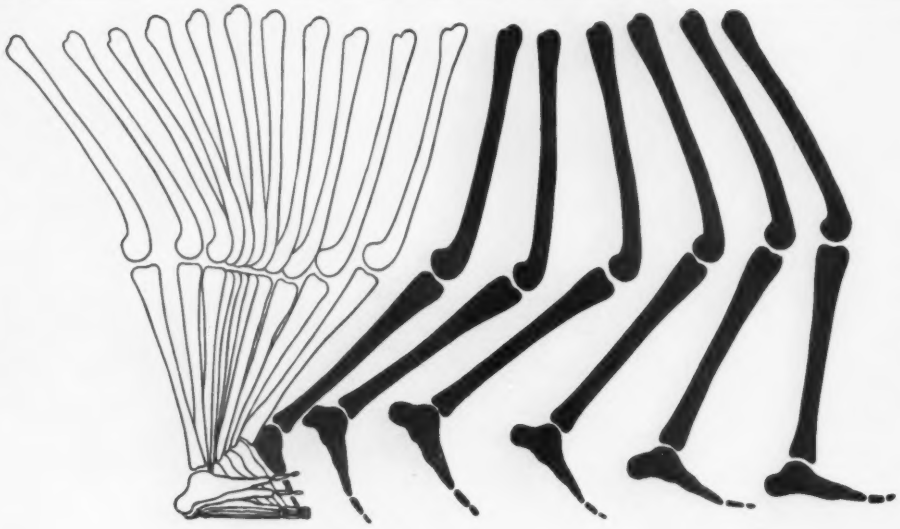
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Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off.
methylprednisolone acetate, Upjohn

The Upjohn Company, Kalamazoo, Michigan

Upjohn

relief within hours... lasting for weeks

Depo-Medrol* intra-articularly

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CAPLA™
(mebutamate, Wallace)
CENTRAL ACTING PRESSURE LOWERING AGENT

ANNOUNCING

CAPLA™

A new drug that works in a new way to control blood pressure without serious side effects

CAPLA™

(mebutamate, Wallace)

CENTRAL ACTING PRESSURE LOWERING AGENT

Capla acts centrally at the brainstem vasomotor center

Reduces blood pressure by central action; is not a ganglionic blocker

Capla is a new *kind* of drug to treat hypertension. Chemically, Capla is 2-methyl-2-*sec*-butyl-1, 3-propanediol dicarbamate. It is unrelated chemically to any other antihypertensive agent. Capla does not block ganglia, reduce blood volume or interfere with neurohormonal balance.

New therapy for hypertension

Because of its action at the brainstem vasomotor control center, Capla is a new therapy for hypertension. It is effective alone in the treatment of mild to moderate hypertension, and can be combined with diuretics or peripherally acting antihypertensives in more severe cases.

Exceptionally well tolerated

Capla acts rapidly, producing substantial blood pressure reduction within two hours, yet it does not produce postural hypotension. It has proved exceptionally well tolerated in clinical use and has no known contraindications. Capla has not produced changes in renal, hematological, hepatic or endocrine function. It is rapidly eliminated and has no cumulative effects.

CAPLA™

(mebutamate, Wallace)

CENTRAL ACTING PRESSURE LOWERING AGENT

Controls blood pressure without serious side effects

Capla does not produce depression, postural hypotension, nasal congestion or gastric hyperacidity

Capla helps minimize one of the most difficult problems of hypertension therapy – unwanted and often serious side effects.

With Capla you have effective therapy without the unpleasant side effects which often cause patients to abandon treatment.

Side effects with Capla, when they do occur, are mild and usually transient. Transient drowsiness sometimes occurs, usually at higher dosage.

Mild calming effect

Patients on Capla often report a mild calming effect. This effect, together with the unusual freedom from serious side effects, makes therapy gratifying for both the patient and the physician.

Compatible with other drugs

Hypertensive patients with other disorders can receive Capla along with other medications.

For example, patients with congestive heart failure, angina, and diabetes mellitus can receive Capla along with such medications as digitalis, nitrates, and insulin—without aggravating these other disorders.

CAPLA™

(mebutamate, Wallace)

CENTRAL ACTING PRESSURE LOWERING AGENT

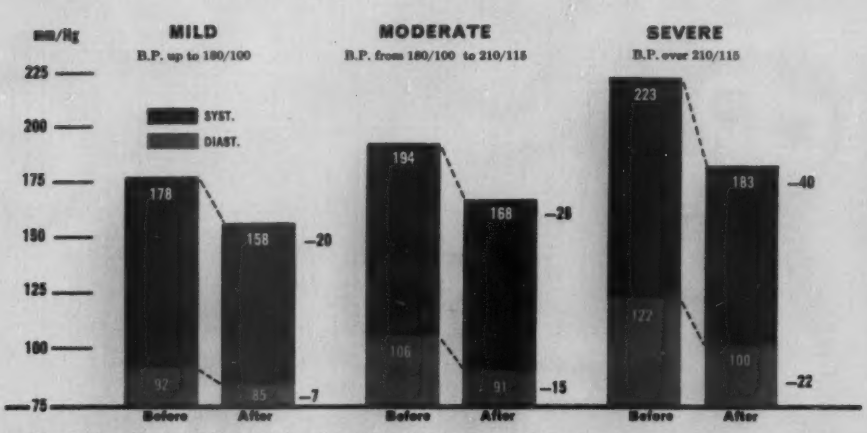
Lowers blood pressure effectively in clinical use

CLINICAL & PHARMACOLOGICAL REPORTS

1. Berger, F. M., and Margolin, S.: A Centrally Acting Blood Pressure Lowering Agent (W-583). Fed. Proc. 20:113 (March) 1961. 2. Diamond, S., and Schwartz, M., Scientific Exhibit at Ill. State Med. Soc. Chicago, (May) 1961. 3. Douglas, J. F., Ludwig, B. J., Ginsberg, Y. and Berger, F. M.: Studies on W-583 Metabolism. Fed. Proc. 20:113 (March) 1961. 4. Duarte, C., Brest, A. N., Kodama, R., Naso, F., and Moyer, J. H.: Observations on the Antihypertensive Effectiveness of a New Propanediol Dicarbamate (W-583). Curr. Ther. Res., 2:148-52 (May) 1960. 5. DuChez, J. W., Scientific Exhibit at Amer. Academy of Gen. Practice, Miami, (April) 1961. 6. Kletzkin, M., and Berger, F. M.: A Centrally Acting Antipressor agent. Fed. Proc. 20:113 (March) 1961. 7. Mulinos, M. G., Scientific Exhibit at Amer. Coll. Card. New York, (May) 1961. 8. Mulinos, M. G., Saltefors, S., Boyd, L. J. and Cronk, G. A.: Human Pharmacology Studies with W-583. Fed. Proc. 20:113 (March) 1961. 9. Shubin, H., Scientific Exhibit, Amer. Coll. Card. New York, (May) 1961.

Average Reductions In Systolic And Diastolic Blood Pressure Reported With Capla

(325 patients)



Usual dose, Capla 300 mg., q.i.d.—duration of therapy, 3 weeks to over 1 year.

These data show that Capla reduces both systolic and diastolic blood pressure, usually in proportion to initial pre-treatment elevations.

DOSAGE: the recommended dose of Capla is one 300 mg. tablet three or four times daily, before meals and at bedtime. The dosage should be adjusted to individual requirements; for example, older patients may require lower dosage.

COMPOSITION: each white, scored tablet contains 300 mg. of Capla (mebutamate, Wallace).

SUPPLIED: bottles of 100, scored tablets.

Literature and samples to physicians on request.

CAPLA™

CENTRAL ACTING PRESSURE LOWERING AGENT

® Wallace Laboratories

Cranbury, New Jersey

Dulcolax®

brand of bisacodyl tablets and suppositories

the laxative with a bibliography

Geigy



The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation
The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

Predictable Action
With Dulcolax tablets action is almost invariably obtained overnight... with suppositories action occurs within the hour.

Wide Application
Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York DU 568-60

new anadrol®

reverses the wasting process-provides solid weight gain

Dosage and administration—Adults: Anadrol is administered orally. The usual adult dosage is 2.5 mg. three times daily. The majority of patients show a favorable result at 7.5 mg./day. However, because of its comparatively low degree of androgenicity, doses up to 15 mg./day may be employed. Results have been seen in 10 days, but optimal results are usually obtained in 4 to 6 weeks. Therapy may have to be continued to sustain improvement according to the needs of the individual patient. **Children:** Adequate response has been observed in children up to the age of 12 years on dosage schedules of 2.5 mg./day and 5 mg./day. Children over 12 years of age may be given adult doses.
Precautions—Side effects with Anadrol have been minimal when administered in the recommended daily dosage range. In those few instances where masculinizing effects have been noted in adults or children, reversal has been accomplished after discontinuing therapy. Although Anadrol exhibits only a slight androgenicity, it shares with all androgens a tendency to favor sodium retention. For this reason, the drug should be used with caution in patients with heart disease. Administration to children should not be continued beyond a 30-day period because of increased sensitivity to masculinizing agents. If such masculinizing symptoms develop, this drug should be discontinued.
Contraindications—Anadrol is contraindicated in the presence of carcinoma of the prostate and, because of changes which have been observed in hepatic function on long-term use with Anadrol at higher doses, it should be used with caution in patients with known hepatic damage. It is also contraindicated in nephritis and nephrosis.
How supplied—Anadrol 2.5 mg. is supplied in bottles of 50 white, monogrammed tablets.

PRODUCT BROCHURE
ON REQUEST

anadrol
oxymetholone, Syntex

ANABOLIC STEROID

reverses the wasting process—provides solid weight gain

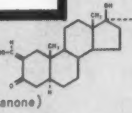
- **Anadrol stimulates nitrogen retention with 4 times the potency of methyltestosterone.***
- **Anadrol produces solid weight gain, not transient fluid retention.**
- **Anadrol is half as androgenic as methyltestosterone.***
- **Anadrol (oxymetholone) is lower in virilization.***
- **Anadrol, because of minimal side effects, is ideally suited for prolonged therapy.**
- **Anadrol is indicated for use in malnutrition and a wide range of catabolic disorders marked by a negative nitrogen balance.**

*As determined in man

this preparation for use in:

Geriatric debilitation	Convalescence from infection
Chronic underweight	Gastrointestinal disease
Pre- and postoperative conditions	General catabolic conditions
Osteoporosis	Malnutrition

anadrol



(2-hydroxymethylene-17α-methyl-17β-hydroxy-3-androstanone)

an original steroid from Syntex



SYNTEX

61 SU-1



to prevent pain and anxiety in angina

For your angina patients, EQUANITRATE helps control pain and angina-triggering anxiety. EQUANITRATE reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerine dependence. Russek† reports "The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE] in the patients studied."

For further information on the limitations, administration, and prescribing of EQUANITRATE, see descriptive literature or current direction circular.

†Russek, H.I.: Am J. Cardiol. *3*:547 (April) 1959.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

Wyeth Laboratories Philadelphia 1, Pa.

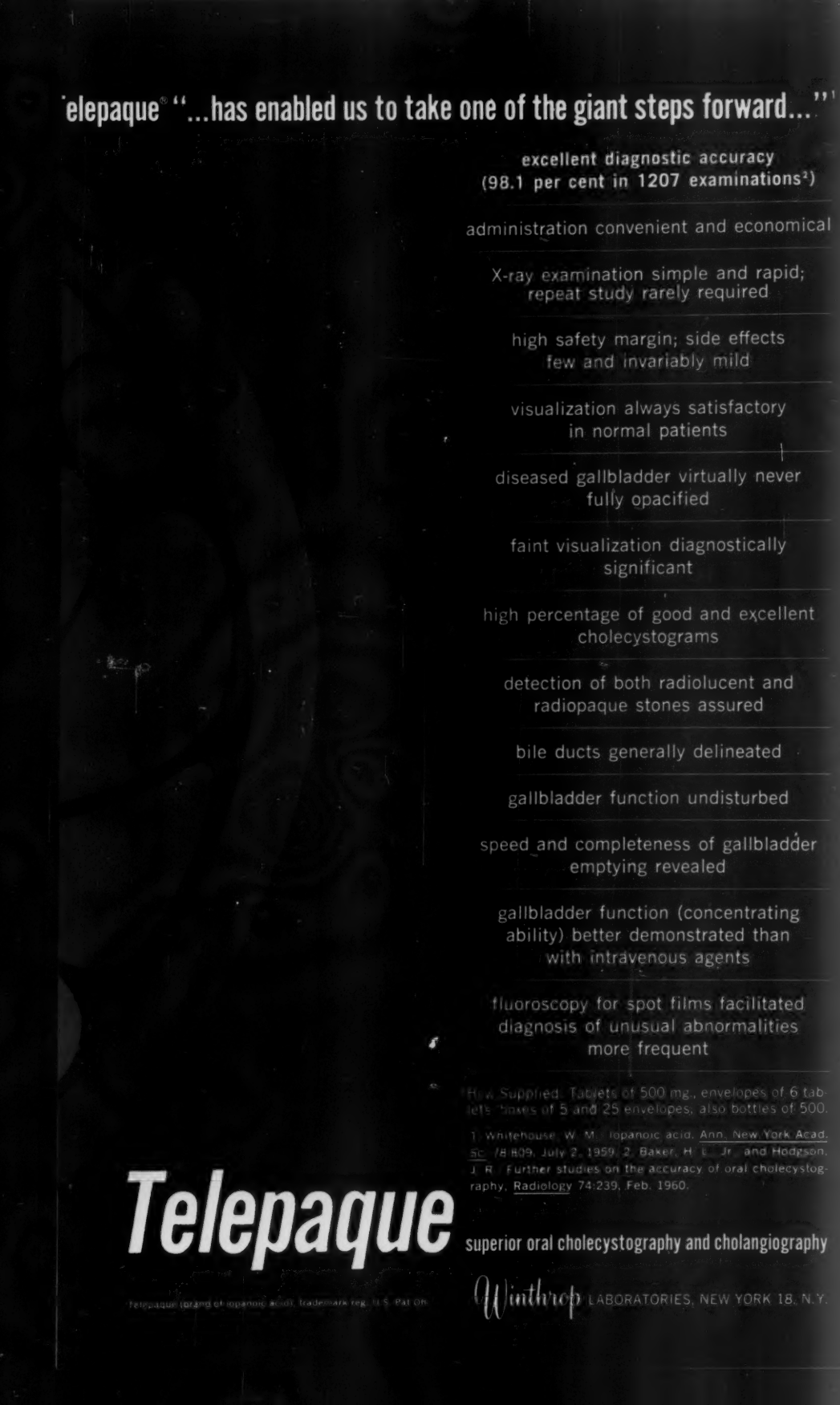
Wyeth SERVICE TO MEDICINE

Equanitrate®

Meprobamate and Pentaerythritol Tetranitrate, Wyeth



Illustration:
Cross-section of body
X-rays passing through
to plate at base



Telepaque® "...has enabled us to take one of the giant steps forward..."[1]

excellent diagnostic accuracy (98.1 per cent in 1207 examinations[2])

administration convenient and economical

X-ray examination simple and rapid; repeat study rarely required

high safety margin; side effects few and invariably mild

visualization always satisfactory in normal patients

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bile ducts generally delineated

gallbladder function undisturbed

speed and completeness of gallbladder emptying revealed

gallbladder function (concentrating ability) better demonstrated than with intravenous agents

fluoroscopy for spot films facilitated diagnosis of unusual abnormalities more frequent

How Supplied: Tablets of 500 mg., envelopes of 6 tablets, boxes of 5 and 25 envelopes, also bottles of 500.

1. Whitehouse, W. M.: Iopanoic acid. Ann. New York Acad. Sc. 78:809, July 2, 1959. 2. Baker, H. L., Jr., and Hodgson, J. R.: Further studies on the accuracy of oral cholecystography. Radiology 74:239, Feb. 1960.

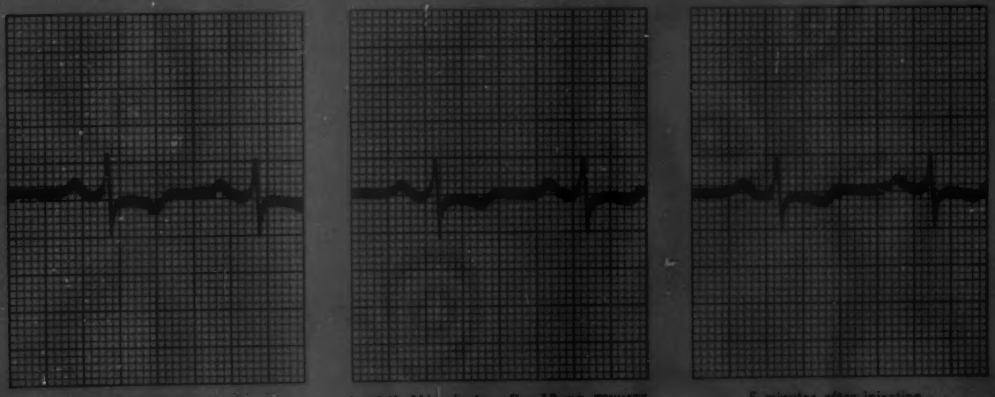
Telepaque

superior oral cholecystography and cholangiography

Telepaque (brand of iopanoic acid). Trademark reg. U.S. Pat. Off.

Winthrop LABORATORIES, NEW YORK 18, N.Y.

for overweight cardiacs/hypertensives... Rx the anorexic with no reported contraindications



Lead II: at rest.

Lead II: 1½ minutes after 10 mg. TENUATE i.v.—equivalent to 100 mg. oral dose (4 times the recommended oral dose).

5 minutes after injection.

with Tenuate, ECG fluctuation is insignificant[1]

TENUATE

(diethylpropion)

hunger control with less than 1% CNS stimulation[2-5]

TENUATE suppresses appetite with unique advantages for "special risk" patients: no effect on heart rate, blood pressure, pulse or respiration,[1] no alteration of BMR.[2]

Dosage: One 25 mg. Tablet one hour before meals, or 1 new TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

Supply: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

References: 1. Alfaro, R.D., Gracanin, V. and Schlueter, E.: J. Lancet *80*:526, 1960. 2. Husis, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Horwitz, S.: Personal communication, 1959. 4. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 5. Ravets, E.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Decina, L. J.: Exper. Med. & Surg. *(in press)*. 7. Sessinan, J.S.: Personal communication, 1959. 8. Krooss and Storck: Personal communication, 1959.

NOW TENUATE DOSPAN
10 TO 12 HOUR HUNGER CONTROL WITH 1 TABLET

Brochure with full product information available on request.

Merrell SINCE 1828

THE WM. S. MERRELL COMPANY
Division of Richardson-Merrell Inc.
Cincinnati, Ohio • Weston, Ontario

TRADEMARKS: TENUATE®, DOSPAN® (SUSTAINED CONTINUOUS RELEASE DOSAGE FORM)



Kills pain.....stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions—new compound of Soma, phenacetin and caffeine kills pain, stops tension, reduces fever—gives more complete relief than other analgesics . . . acts fast, relief lasts four to six hours

Composition: 200 mg. Soma (carisoprodol), 160 mg. phenacetin, 32 mg. caffeine. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 apricot-colored, scored tablets.

Also Available As
SOMA COMPOUND + CODEINE

Soma Compound boosts the effectiveness of codeine. SOMA COMPOUND + CODEINE therefore contains only ¼ grain of codeine phosphate to relieve the more severe pain that usually requires ½ grain. Otherwise, its composition—and dosage—is the same as Soma Compound. Supplied in bottles of 50 white, lozenge-shaped tablets.

soma® Compound

CSO-5163

WALLACE LABORATORIES/Cranbury, N.J.

new Azo-Mandelamine

THE URINE-SPECIFIC ANALGESIC-ANTIBACTERIAL

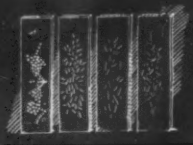
in common lower urinary infections



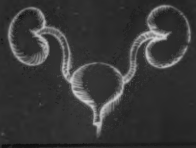
controls urinary infection without producing resistant mutants



relieves urinary pain in 30 minutes



effective against most urinary pathogens



active only in the urinary tract



sensitization and other systemic reactions do not develop



well tolerated

WARNER CHILCOTT

MORRIS PLAINS, N.J.

Composition: Each Azo-Mandelamine tablet contains 50 mg. phenylazodiamino-pyridine HCl (Pyridium®) and 500 mg. methenamine mandelate (Mandelamine®). **Average Adult Dosage:** Two Azo-Mandelamine tablets four times a day. **Precautions:** Azo-Mandelamine is contraindicated in patients with renal insufficiency and/or severe hepatitis. An occasional patient may experience gastrointestinal disturbance. Full dosage information, available on request, should be consulted before initiating therapy.

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To New Friendships

Take the problem of Doctor A and Clinic Y, for instance. Doctor A, an able internist, had decided to find a post which held greater promise for the future. No immediate opening offered at the time, but we searched the field and put him in touch with the most suitable positions *then available.*

We pursued our efforts unrelaxed, and the physician candidate cooperated. When Clinic Y, located several states away, asked us to find an internist of qualifications which Doctor A fulfilled, we described the opening to him at once, and he was shortly accepted.

Doctor A told us later how he felt about the solution we found: "Your consistent and untiring attempts to find the position I sought certainly deserve the highest praise." . . . May we help solve YOUR personnel problem?

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RESPONSIVE TO TRIAMCINOLONE

"Triamcinolone has been shown to have more profound anti-inflammatory and antiallergic properties than preceding corticosteroids."*

■ enhanced anti-inflammatory, antipruritic, antiallergic effects ■ less gastrointestinal distress ■ may be of value when other corticoids have failed ■ virtually no mood changes, edema, sodium or water retention, or secondary hypertension

Supply: Scored tablets of 1 mg., 2 mg. and 4 mg. Syrup, in 120 cc. bottles, each 5 cc. teaspoonful containing 5.1 mg. triamcinolone diacetate providing 4 mg. triamcinolone.

*Edelstein, A. J.: Pennsylvania M.J. 62:1831 (Dec.) 1959.

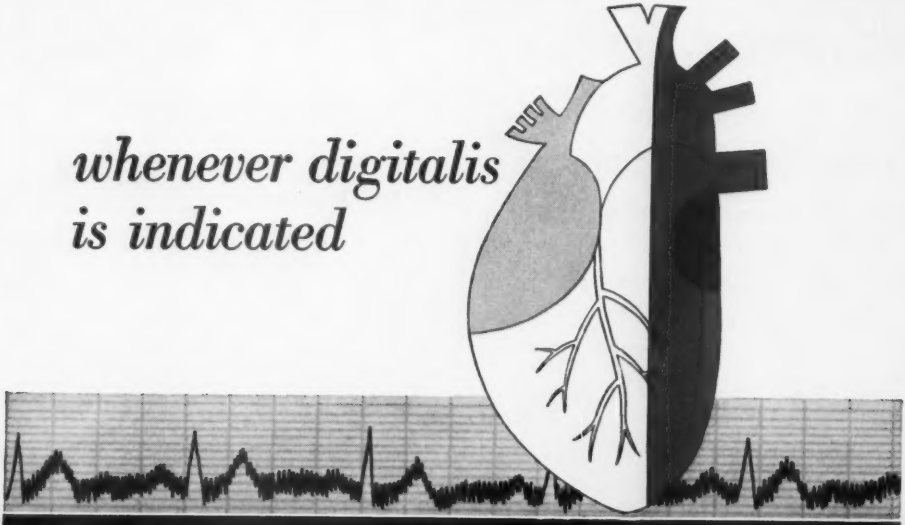
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Squibb Quality—the Priceless Ingredient

Pemphigus vulgaris

whenever digitalis is indicated



'LANOXIN'® brand DIGOXIN

formerly known as Digoxin 'B. W. & Co.'

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

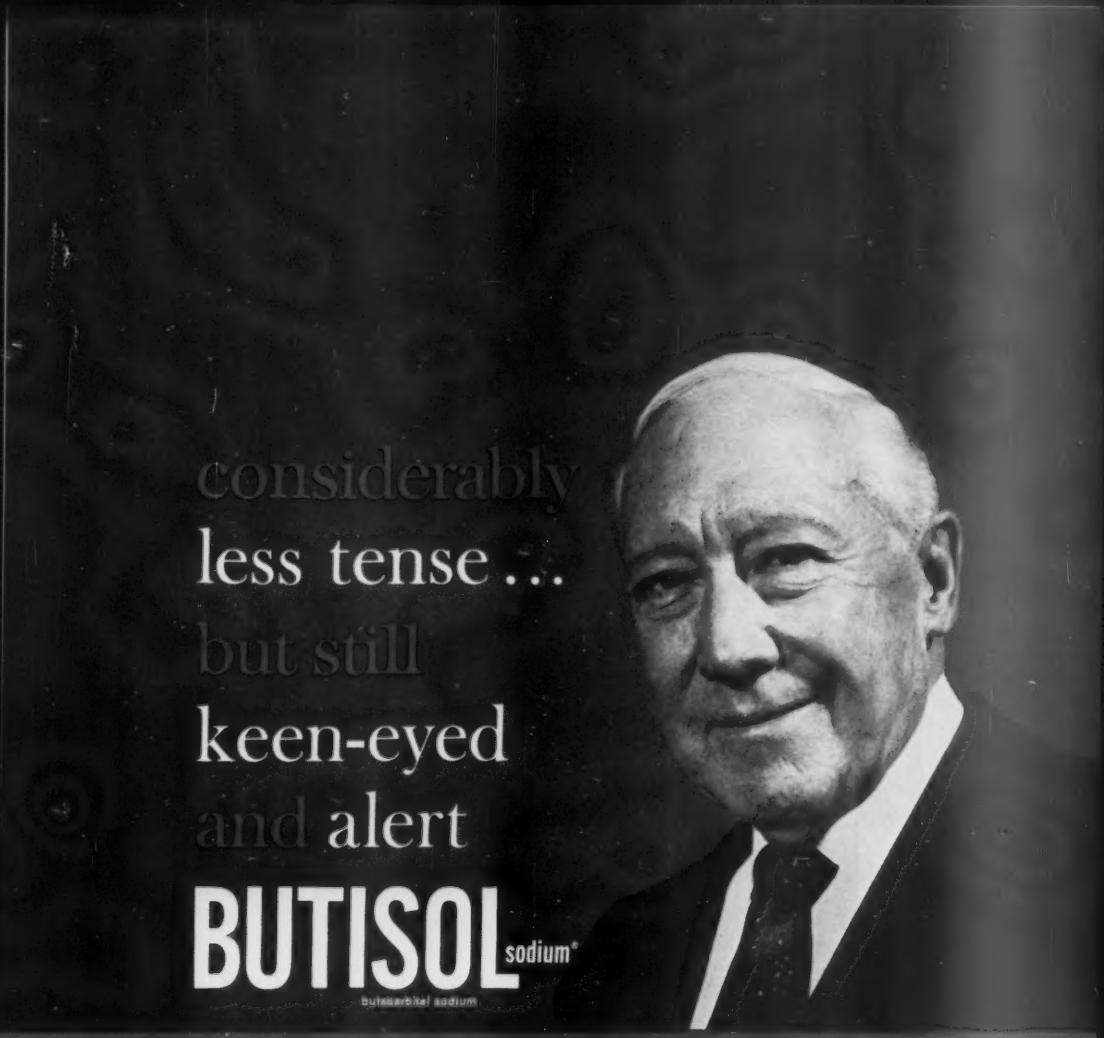
Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS
0.25 mg. scored (white)
0.5 mg. scored (green)

'LANOXIN' INJECTION
0.5 mg. in 2 cc. (I.M. or I.V.)

'LANOXIN' ELIXIR PEDIATRIC
0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.



In a five-year study[1] of representative sedative and ataractic agents, BUTISOL SODIUM provided the highest therapeutic index (per cent of effectiveness: per cent of untoward reactions) for control of anxiety and insomnia by daytime dosage.

"The therapeutic index as defined in this study reflects clinical usefulness and indicates to what degree a sedative agent approaches the ideal."[1] It is significant that phenobarbital, although widely used in anxiety states, falls far short of the ideal.[1]

BUTISOL SODIUM® Tablets
Repeat-Action Tablets
Elixir/Capsules

McNEIL **McNeil Laboratories, Inc.,** Fort Washington, Pa.

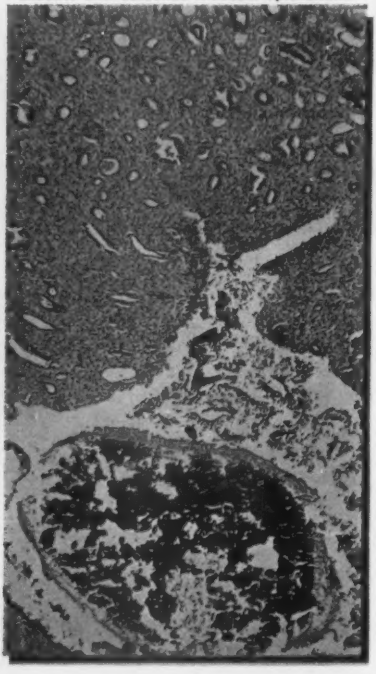
1. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (October) 1959.

GOUT

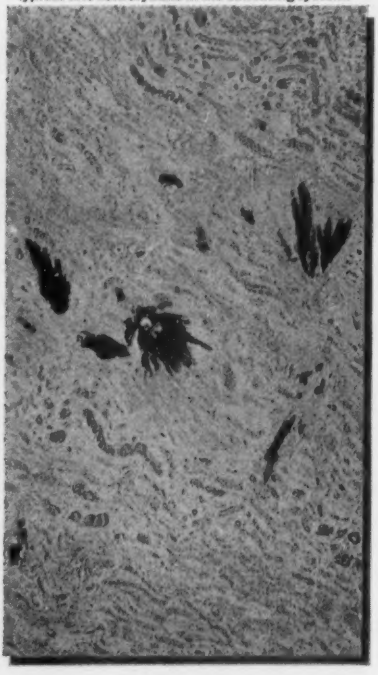
"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."[1]

Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."[2]

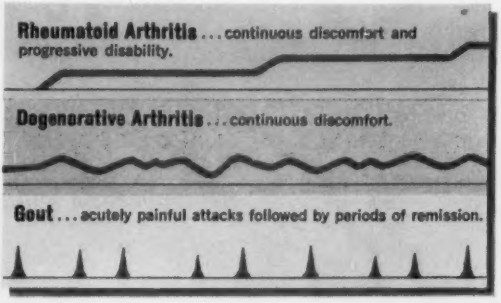
Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.[3]

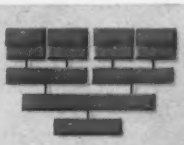


The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.[3]



AIDS TO DIAGNOSIS





"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."[4]



"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."[6]



"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."[8]



Colchicine test: "Colchicine should be administered as early as possible after the onset of articular distress, 1 mg.... every 2 hours until the onset of gastro-intestinal distress. From 5 to 8 mg. usually are required."[9] Pain relief is highly indicative of gout.

THE "INSULIN OF GOUT"[7]

"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."[8]

BENEMID®

PROBENECID

Therapy with BENEMID should be continued without interruption since hyperuricemia recurs when dosage is terminated. The rare patient who experiences gastric discomfort is usually benefited by decreasing the dosage. Dosage: 0.25 Gm. twice daily for one week, followed by 1 Gm. daily in divided doses. Supply: 0.5 Gm. tablets.

A COMPLEMENTARY FORMULATION OF TWO CLASSIC ANTI-GOUT AGENTS

"... the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[9]

ColBENEMID®

COLCHICINE WITH BENEMID

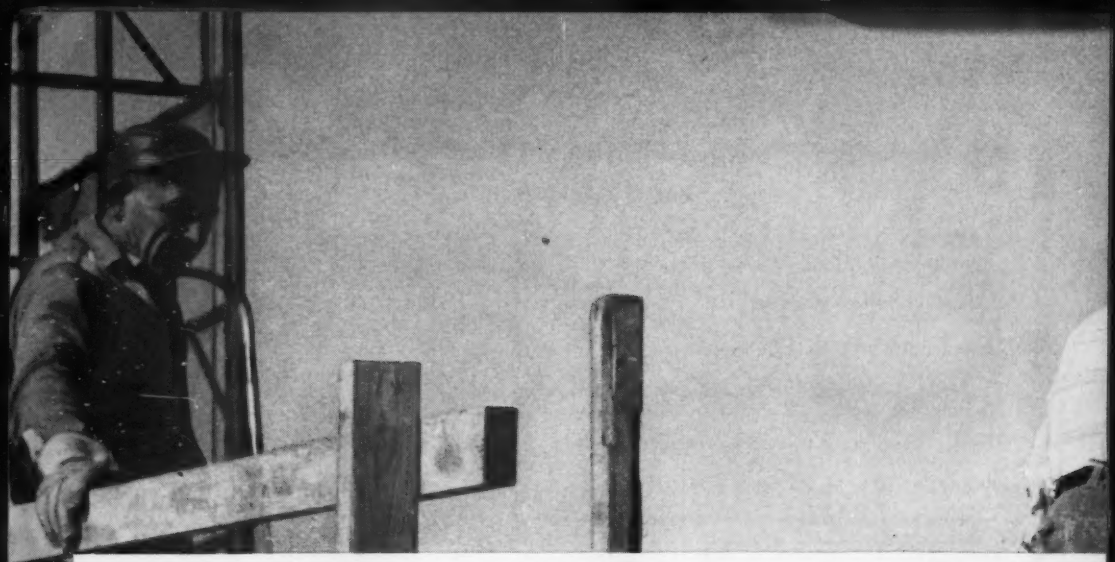
Dosage: One tablet daily for one week, followed by one tablet twice daily. Supply: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100 and 1000.

1. Cornish, A. L.: J. Kentucky M.A. 58:707, June, 1960. 2. Wyngaarden, J. B.: Arthritis & Rheumatism 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: Medicine 39:405, Dec., 1960. 4. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: J. Chron. Dis. 2:645, Nov., 1955. 6. Hench, P. S.: Gout and gouty arthritis, in Cecil, R. L.: A textbook of medicine, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kepkay, P. H.: Bull. Vancouver M.A. 29:306, April, 1953. 8. Boland, E. W.: World-Wide Abstracts of Gen. Med. 3:16, Jan., 1960. 9. Talbott, J. H.: Current Med. Dig. 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.

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Soma's prompt relief of pain and stiffness can get your low-back patients back to work in days instead of weeks

Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in *a single drug*. Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

Thus with Soma, you can break up both pain and spasm fast, effectively . . . help give your patient the two things he wants most: relief from pain and rapid return to full activity.

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only with higher dosages. Soma is available in 350 mg. tablets. USUAL DOSAGE: 1 TABLET Q.I.D.

The muscle relaxant with an independent pain-relieving action

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(carisoprodol, Wallace)

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How you can help save your patients a month's pay

Kestler reports in J.A.M.A. (April 30, 1960) that conventionally treated low-back syndrome patients required an average of 41 days for full recovery (range: 3 to 90 days). The addition of Soma therapy in this comparative investigation reduced the average to 11.5 days (range: 2 to 21 days). With Soma, patients averaged full recovery 30 days sooner.

only 2 seconds to specify MAXIMUM QUALITY

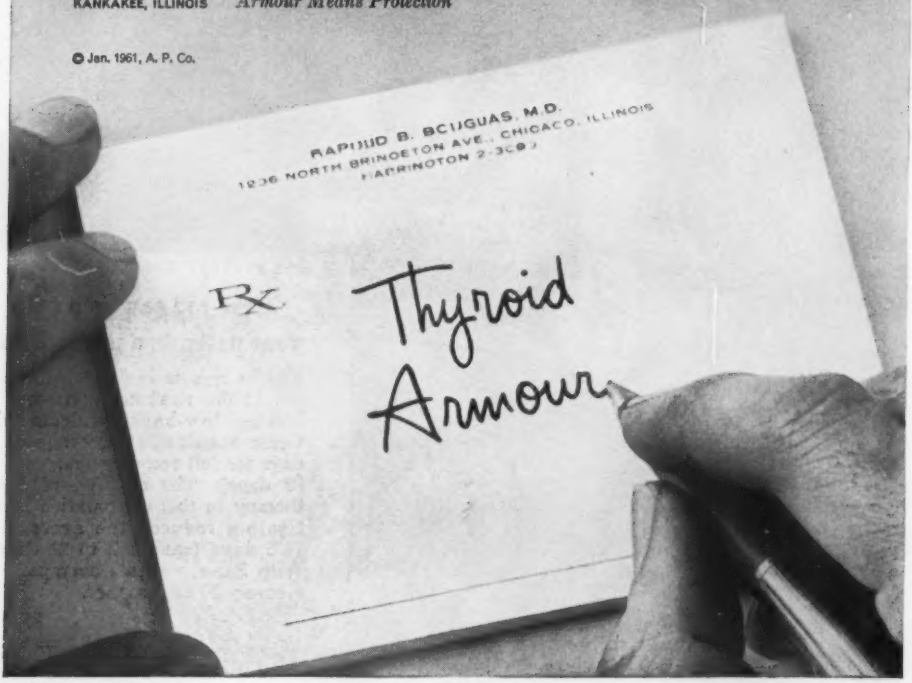
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Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (non-toxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger: potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.

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physiologic anti-fatigue agent

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SPARTASE provides *natural, physiologic* treatment for fatigued patients. It may be used either alone in functional disorders or, adjunctively, in the presence of organic disease.

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In selected cases, SPARTASE restores normal work capacity.

Tablets

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Potassium and Magnesium Aspartates, Wyeth

OFFICIAL BROCHURE

SPARTASE is a mixture of equal amounts of the potassium and magnesium salts of aspartic acid. Pharmacological and clinical observations have been made which indicate that SPARTASE participates in intermediary metabolism in such a fashion as to be effective therapeutically in the management of fatigue.

General Pharmacological Properties—The IP and PO LD_{50} values for SPARTASE in rats are 4 and 19 grams/kg., respectively.

The pharmacological activity of aspartic acid has been the subject of numerous publications[1-8] and need not be reviewed.

Laborit *et al.*[9,10] studied the effects of the combined K and Mg aspartates on groups of white rats subjected to the standard swim test. It was found that duration of swim after this therapy was significantly prolonged over that achieved with other regimens attempted. After a standard rest period of 2½ hours, the aspartate-treated animals again swam longer than any other group.

Plasma ammonia levels were measured in groups of rats similarly exposed to swim effort and drug therapy. Increase in ammonia levels noted in the controls[11] was not seen in the group pretreated with the aspartates.

A group of 16 dogs breathing a mixture of 90% oxygen and 10% CO_2 was given the combined salts of aspartic acid parenterally. Plasma and expired CO_2 tension decreased, and plasma urea concentration increased immediately[12].

The administration of K and Mg aspartates to athletes demonstrated a positive effect on neuro-muscular irritability, a significant reduction in existing fatigue and a significant prophylactic effect against the induction of fatigue[10,13,14].

Indications—The use of SPARTASE for the treatment of fatigue is not intended to supplant specific treatment for accompanying organic disease or to substitute for specific indications for potassium.

SPARTASE has a wide range of clinical utility in the management of the fatigue syndrome. It may be used effectively in the management of many fatigue problems, whether or not associated with functional or organic disease. SPARTASE is particularly useful in treating the tired patient with no evidence of organic dysfunction.

Dosage and Administration—The adult dose of SPARTASE is two 500 mg. tablets after the morning and evening meals. Approximately four days therapy are required before subjective clinical improvement may be noted; it is suggested that SPARTASE administration be continued for at least two weeks before the patient is re-evaluated.

Contraindications and Side Effects—Nausea, abdominal discomfort and diarrhea have been noted occasionally. These symptoms may be minimized by proper administration of dose after meals.

There are no known contraindications to SPARTASE therapy.

References—1. H. Kamin, P. Handler: J. Biol. Chem. *193*:873-80 (1951). 2. H. Resnik, M.F. Mason: Am. J. Med. Sci. *192*:520-5 (1936). 3. J.A. Brockman, Jr., S.L. Burson, Jr.: Proc. Soc. Exptl. Biol. Med. *94*:450-2 (1957). 4. H.H. Tallan: J. Biol. Chem. *224*:41-5 (1957). 5. B.J. Miller, V. W. Ciacci, S. P. Reimann: Growth *5*:329-50 (1941). 6. S. Edlbacher, K. Schmid: Helv. Chim. Acta *28*: 1079-88 (1945). 7. D.P. Tschudy, M. Marshall, A. Graff, S. Graff: Cancer *11*:984-95 (1958). 8. M.N. Mickelson, R.S. Flippin: Arch. Biochem. Biophys. *64*:246-8 (1956). 9. H. Laborit, R. Moynier, A. Trzebski, G. Guiot, C. Baron: Compt. rend. soc. biol. *151*:1383-6 (1957). 10. C. Vial: Imprimerie des Tournelles, Paris, 1959. 11. H. Laborit, L. Obrenovitch, P. LeGuen: Compt. rend. soc. biol. *152*:1359-60 (1958). 12. H. Laborit, P. Niaussat, J.M. Jouany, B. Weber, J. Martin, C. Baron: Compt. rend. soc. biol. *152*:1094-7 (1958). 13. Thiebault: Bull. mens. soc. med. mil. franc. *52*:139-49 (1958). 14. H. Laborit, B. Weber, P. Niaussat, J.M. Jouany, G. Guiot, J. Zawadowski, C. Baron: Anesthésie et analgésie *15*:480-94 (1958).

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INDICATIONS: Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

DOSAGE: One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

REFERENCES: From the Symposium, *Recent Concepts of Pain and Analgesia*, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: *Non-Narcotic Analgesia in Ambulatory Patients.* 2. O'Dell, T. B.: *Experimental Parameters in the Evaluation of Analgesics.* 3. Miller, L. D.: *Distribution, Excretion and Metabolic Fate of Phenyramidol.* 4. Beisler, E.: *Preliminary Report of Experience with Phenyramidol for Dental Analgesia.* 5. Bader, G.: *Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators.* 6. Taylor, S. L.: *Phenyramidol in General Hospital Orthopedics.* 7. Bodi, T.: *Pain Management Among Clinic Outpatients.* 8. Ramunis, J.: *Experience of an Industrial Surgeon with Phenyramidol.* 9. Kast, E. C.: *Methodological Considerations in the Clinical Evaluation of an Analgesic.* 10. Collopy, C. T.: *Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients.* 11. Cass, L. J.: *Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain.* 12. Lamphier, T. A.: *Intravenous Phenyramidol in the Management of Low Back Pain and Allied Disorders.* 13. O'Dell, T. B.: Chicago Med. *63*:9, 1961. 14. Kast, E. C.: Chicago Med. *63*:17, 1961. 15. Wainer, A. S.: J. Am. M. Women's A. *16*:218, 1961. 16. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 17. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 18. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 19. O'Dell, T. B., *et a.*.: Fed. Proc. *18*:1694, 1959. 20. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 21. Wainer, A. S.: Clin. Med. *7*:2331, 1960. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

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Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

Diabinese and diet

In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or caloric control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

Diabinese and the insulin patient

DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

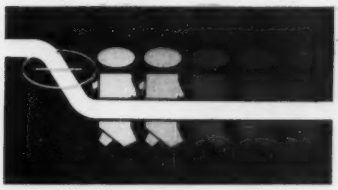
In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.[3] Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.[4]

Diabinese from the start

Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,[5] observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,[6] who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

1. Johnsson, S.: Diabetes 9:1, 1960. 2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960. 3. Editorial: Brit. M. J. 1:188, 1961. 4. Duncan, L. J. P., and Baird, J. D.: Pharmacol. Rev. 12:91, 1960. 5. A.M.A. Council on Drugs: New and Nonofficial Drugs, 1961, Philadelphia, Lippincott, 1961, p. 657. 6. Fineberg, S. K.: J. Am. Geriat. Soc. 8:441, 1960.

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the oral antidiabetic most likely to succeed

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DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

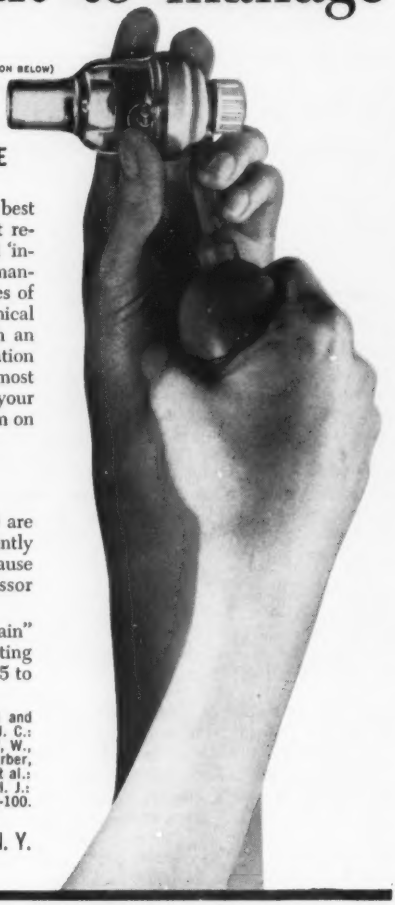
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"nutrition...present as a modifying or complicating factor in nearly every illness or disease state"[1]

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases "Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2] 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis "It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . ."[3]
3. Fernandez-Herlihy, L.: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.[4] Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.[5] 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases "Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult."[6] 6. Overholser, W., and Fong, T. C. C. In Stieglitz, E. J.: Geriatric Medicine, 3rd edition. J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.[7] 7. Goldsmith, G. A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec.10) 1960.

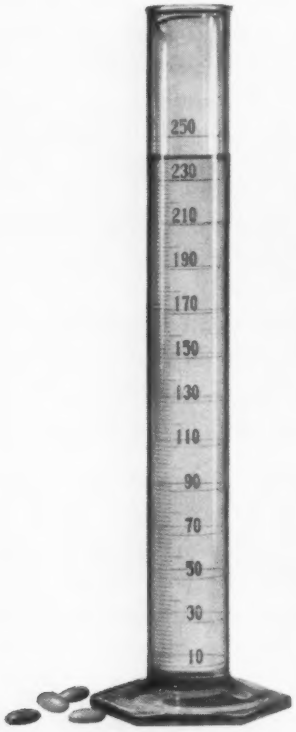
diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.[8] "Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes."[9]
8. Duncan, G. G.: Diseases of Metabolism, 4th edition. W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

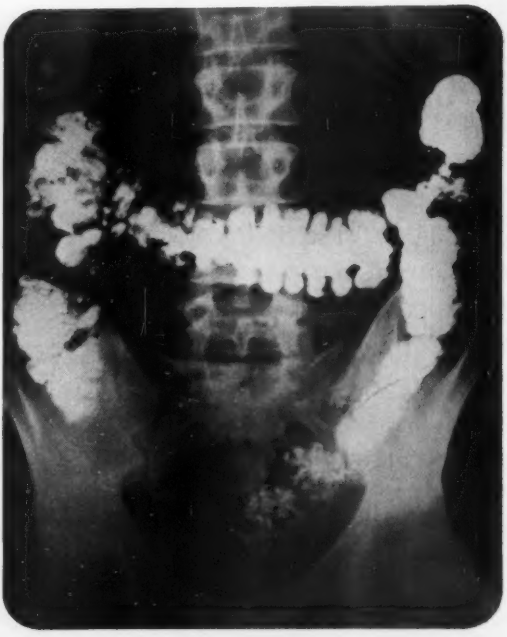
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In acute and chronic diarrhea the most effective symptomatic solution to the dual problem:

dual action **Sorboquel** tablets

(polycarbophil-thihexinol methylbromide)





fast action **1**

for too fluid feces:

Exceptional water-binding capacity of polycarbophil to absorb free fecal water

fast action **2**

for too frequent evacuations:

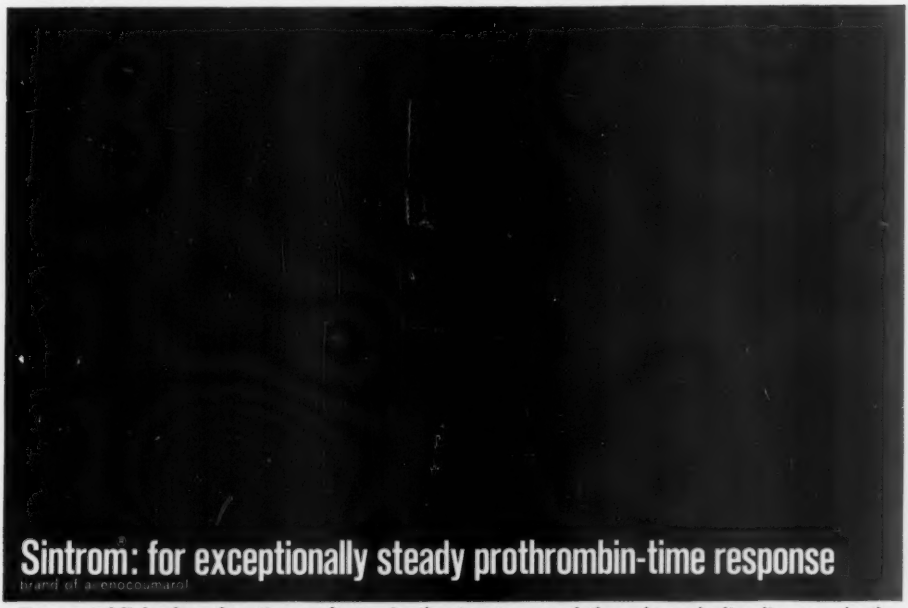
Superior, yet selective, nonopiate antimotility action of thihexinol methylbromide

(Complete information regarding the use of Sorboquel Tablets is available on request.)

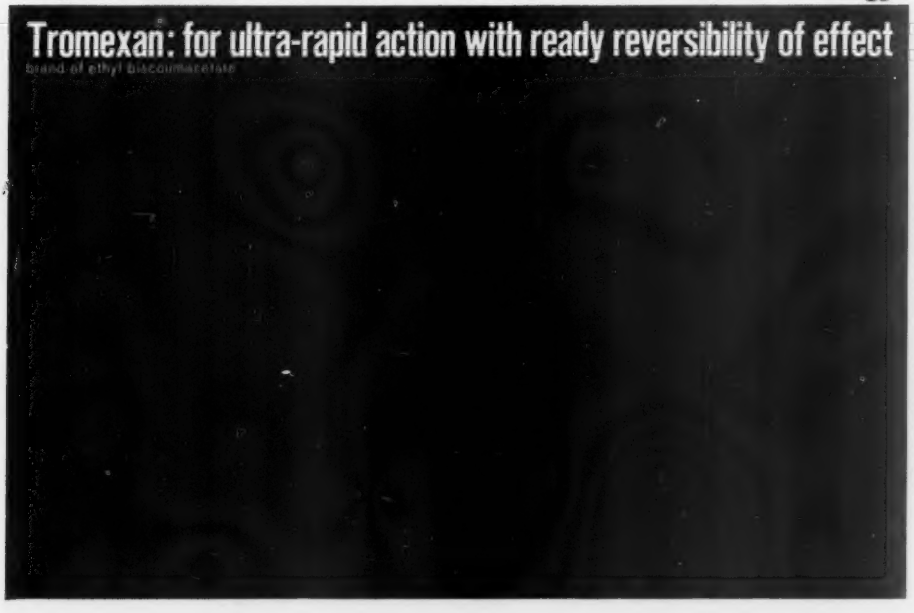
dosage: For older children and adults, initial dosage of one SORBOQUEL Tablet q.i.d. is usually adequate. Severe diarrheas may require six, or even eight, tablets in divided daily doses. (Dosages exceeding six tablets a day should not be employed over prolonged periods.)

Supplied: Sorboquel Tablets, bottles of 50 and 250. Each tablet contains 0.5 Gm. polycarbophil and 15 mg. thihexinol methylbromide.

WHITE LABORATORIES, INC., Kenilworth, New Jersey White



Two established oral anticoagulants. In the treatment of thromboembolic disease, both Sintrom and Tromexan reliably bring about hypoprothrombinemic response.
Distinguished by high potency and its ability to maintain a uniform response with a constant single daily dose, Sintrom is particularly suited to long-term therapy. Significantly more rapid and transient in action, Tromexan is well adapted to cases calling for more immediate control of thrombotic tendencies.
Full information regarding dosage, side effects, precautions and contraindications available on request.
Sintrom®, brand of acenocoumarol, is supplied as double-scored tablets of 4 mg.
Tromexan®, brand of ethyl biscoumacetate, is supplied as single-scored tablets of 150 and 300 mg.
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York SI/TR-662-61 **Geigy**



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to TRADE up to a new BURDICK EK-III

Is your electrocardiograph more than five years old? If it is, now is the time to trade up to a new Burdick EK-III. You'll get sharper, clearer records. Switching from lead to lead is instantaneous. True high fidelity will be yours with EK-III design that incorporates a more sensitive galvanometer, a new tubular stylus, a new amplifier system. A new console cabinet is available for added convenience and mobility of your ECG equipment.

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Milton, Wisconsin

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Where's the arthritic this morning?



Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	**12 to 16 mg.**	**6 to 12 mg.**
Moderately severe	**8 to 10 mg.**	**4 to 8 mg.**
Moderate	**6 to 8 mg.**	**2 to 6 mg.**
Children	**6 to 10 mg.**	**2 to 8 mg.**

With Medrol Medules, it may be possible to reduce the total daily dose by ½.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Approximately 135 tiny "doses" mean smoother steroid therapy

Each capsule contains:
Medrol (methylprednisolone) 4 mg.
Supplied in bottles of 30 and 100.

Medrol* Medules*

Upjohn

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when you can run an ECG or BMR in the next room . . .



. . . you have *all* the advantages and conveniences of these two diagnostic facilities at your fingertips. Immediate availability of data, firsthand knowledge and control of conditions at the time of the test, and time saved because "outside arrangements" needn't be made, are but a few of the advantages of owning your own electrocardiograph and metabolism tester.

Popular with a great many of your colleagues the world over are two Sanborn® instruments that can give you these diagnostic facilities "in the next room": the 100M "Mobile Viso®" cardiograph and the "Metabulator" metabolism tester. The "Mobile Viso" offers three recording sensitivities, two chart speeds, provision for recording and monitoring other phenomena, and the dependability and ruggedness of modern electronic design. The "Metabulator" also exemplifies simplicity of operation, with "one-level" controls, easily changed charts and CO_2 absorbent, and quick BMR calculation. Both instruments have the proof of years of service and satisfaction to thousands of doctors.

Call your nearest Branch Office or Service Agency — or write Manager, Clinical Instrument Sales, at the main office in Waltham — about the special combination offer on these two instruments.

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but it needn't trigger a respiratory crisis

You can't isolate the patient with chronic respiratory disease from all potential irritants. That is why Choledyl prophylaxis is essential. Taken regularly – daily – Choledyl helps prevent severe respiratory flare-ups by affording continuous relief from debilitating bronchospasm. Throughout long-term use, Choledyl is uniformly effective. And even in older patients, gastric upset and other unwanted effects are rare.

Dosage: Adults – 1 tablet q.i.d. *Supplied:* 200 mg. tablets (yellow), bottles of 100. *Precautions:* Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. Full dosage information, available on request, should be consulted before initiating therapy.

TO AVOID THE CRISIS IN CHRONIC BRONCHITIS, CHRONIC ASTHMA, EMPHYSEMA

CHOLEDYL®

THE CHOLINE SALT OF THEOPHYLLINE

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makers of Tedral Gelusil Proloid Peritrate Mandelamine MORRIS PLAINS, N.J.

when your patient needs
a potent steroid... simplified control
of subacute or chronic disease...

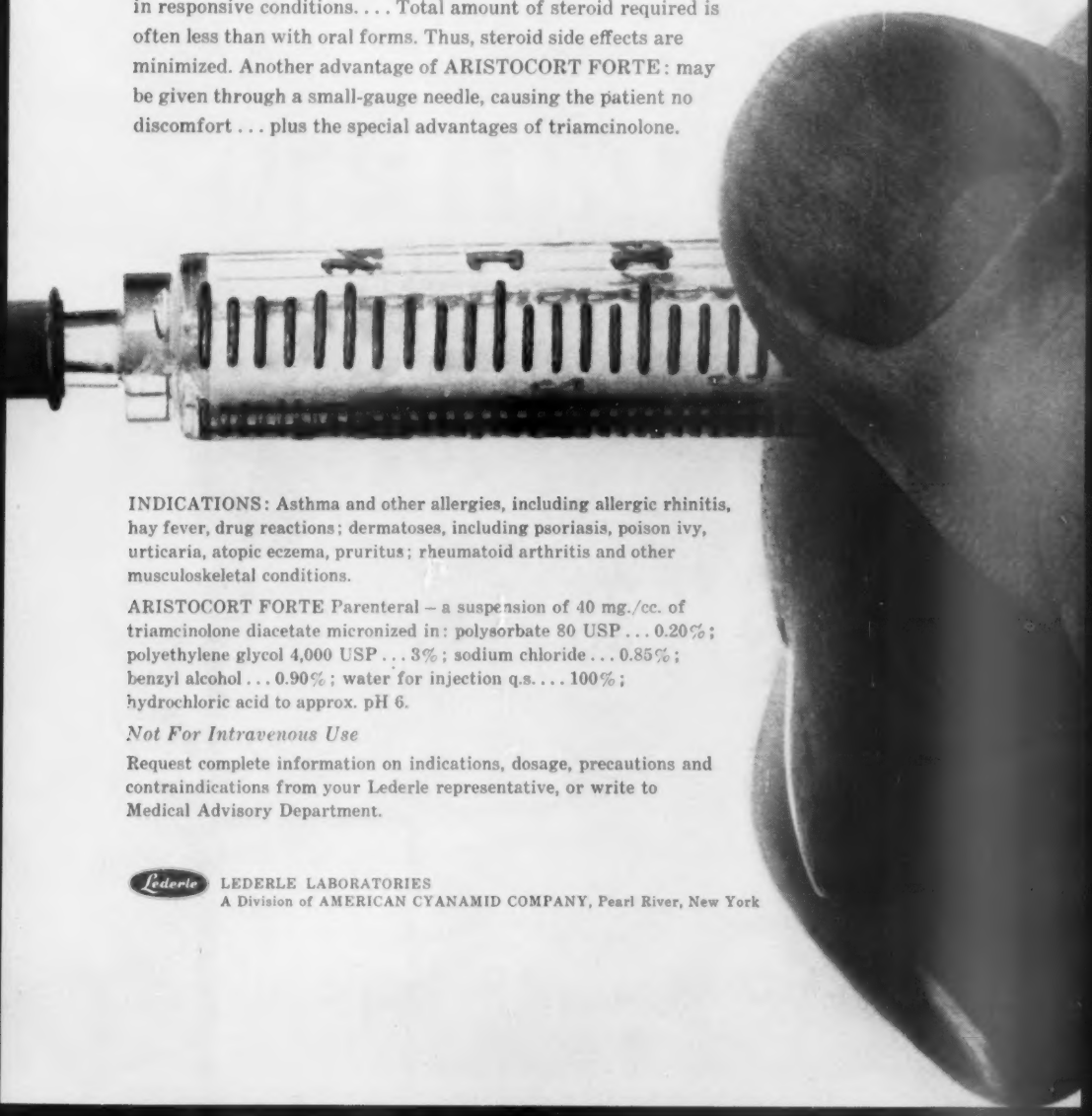
New Aristocort® Forte

TRIAMCINOLONE

Diacetate Parenteral Suspension Lederle

highly effective repository action with single, or infrequent, I.M. injections

Single I.M. doses of ARISTOCORT FORTE 4 to 7 times the usual daily oral dose can control symptoms 4 to 7 days, or even longer—sometimes up to 4 weeks in responsive conditions. . . . Total amount of steroid required is often less than with oral forms. Thus, steroid side effects are minimized. Another advantage of ARISTOCORT FORTE: may be given through a small-gauge needle, causing the patient no discomfort . . . plus the special advantages of triamcinolone.



INDICATIONS: Asthma and other allergies, including allergic rhinitis, hay fever, drug reactions; dermatoses, including psoriasis, poison ivy, urticaria, atopic eczema, pruritus; rheumatoid arthritis and other musculoskeletal conditions.

ARISTOCORT FORTE Parenteral – a suspension of 40 mg./cc. of triamcinolone diacetate micronized in: polysorbate 80 USP . . . 0.20%; polyethylene glycol 4,000 USP . . . 3%; sodium chloride . . . 0.85%; benzyl alcohol . . . 0.90%; water for injection q.s. . . . 100%; hydrochloric acid to approx. pH 6.

Not For Intravenous Use

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

Lederle LEDERLE LABORATORIES
A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

SAFE AND SOUND IN ANY PREGNANCY

to prevent morning sickness

With new Tigan 250-mg capsules you can provide safe, effective protection against morning sickness with only two capsules daily —one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding phenothiazine risks and the drowsiness which often accompanies the antihistamines, Tigan acts prophylactically and therapeutically to stop nausea as well as active vomiting. *Consult literature and dosage information, available on request, before prescribing.*

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride

ROCHE
LABORATORIES Division of Hoffmann-La Roche Inc.

Tigan 250 mg



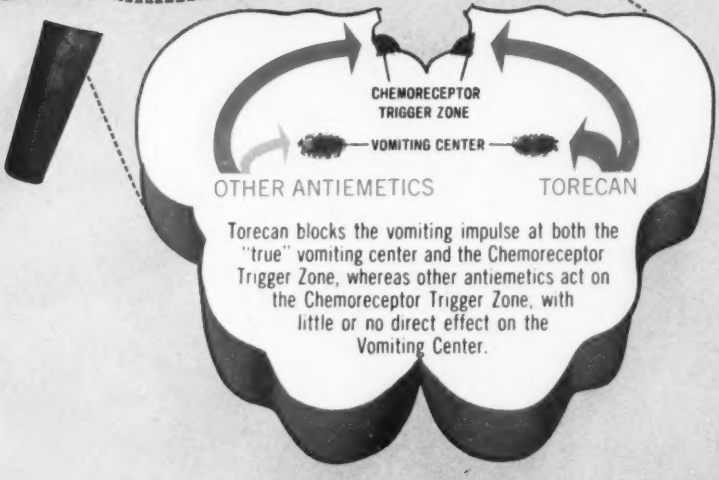


When the rhythm is wrong...PRONESTYL® HYDROCHLORIDE

Announcing...a "broadening of the antiemetic spectrum of effectiveness"[1]



Vomiting is activated by stimulation of the Vomiting Center, either directly or through the Chemoreceptor Trigger Zone.



"Thiethylperazine dimaleate [TORECAN] inhibits apomorphine vomiting [apomorphine elicits vomiting solely through the Chemoreceptor Trigger Zone[2,3,4]] in an even more pronounced manner than the well-known strong antiemetic, prochlorperazine. Thiethylperazine dimaleate also antagonizes oral copper sulfate [copper sulfate may activate the Vomiting Center directly or may act via the Chemoreceptor Trigger Zone]. Interestingly, only slightly higher dosages are needed for this than for the inhibition of apomorphine vomiting, whereas far higher dosages are required of other phenothiazines. This peculiarity of thiethylperazine of influencing not only the trigger zone, but also the vomiting center is of much therapeutic interest because of the broadening of the antiemetic spectrum of effectiveness."[1]

"When evaluating new antiemetic agents, it is necessary to pay close attention to the associated effects on the central and autonomic nervous systems. The aim is to find agents which will specifically depress the emetic mechanism with minimal effects elsewhere."[4]

TORECAN

provides specific antiemetic action with minimal "spillover" effects:

Tranquilizing or sedative action	Insignificant
Potentiation of sedative and anesthetic drugs	Only slight potentiation; less than with other phenothiazine antiemetics
Extrapyramidal symptoms, such as motor restlessness, muscular rigidity, parkinsonism, etc.	None reported at dosage levels of 30-50 mg. per day
Cardiovascular effects (hypotension, cardiac acceleration)	Rare; less than with other phenothiazine antiemetics
Liver, blood, or renal toxicity	None reported
Other side effects: dizziness, dry mouth, weakness, fatigue, blurring of vision, headache, insomnia, constipation or diarrhea	Rare

"an extremely effective antiemetic in a large number of clinical conditions"[5]

Nausea and Vomiting of Pregnancy[6]

Nausea and Vomiting Associated with Gastroenteritis and Colitis[5,6,7]

Nausea and Vomiting due to Radiation and Nitrogen Mustard Therapy[1]

Postoperative Nausea and Vomiting[5]

Nausea and Vomiting Associated with Miscellaneous Non-inflammatory Conditions[5,6,7]

Nausea and Vomiting Associated with Labyrinthine Disturbances

Prophylactic and Therapeutic Dosage: Oral: 1 tablet 3 times daily
Intramuscular: 10-20 mg. daily

Supply: Tablets, 10 mg.; Ampuls, 2 cc. (10 mg.), each cc. contains 5 mg.

Precautions: It is obvious that, before using an antiemetic, clinical judgment must be exercised in determining whether vomiting represents a warning of organic abnormality and that this must first be recognized before employing a potent antiemetic such as TORECAN. Drowsiness and/or dryness of the mouth may occur with doses above 30 mg. daily. While no hepatic, hematopoietic or renal toxicity have been reported at recommended dosage levels, it should be remembered that these reactions may occur with phenothiazines. Orthostatic hypotension may be manifested at higher dose levels. TORECAN is contraindicated in severely depressed or comatose states. In excessive doses, TORECAN may produce extrapyramidal stimulation with the varied symptom complex characteristic of this complication. Ampuls are recommended for **intramuscular injection only.**

References: 1. Codiga, V. A.: A new antiemetic for the treatment of nausea and vomiting associated with roentgen therapy, Int. Rec. Med., 174:375 (June) 1961. 2. Wang, S. C. and Borison, H. L.: The vomiting center: its destruction by radon implantation in dog medulla oblongata, Am. J. Physiol. 166:712 (1951). 3. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, Gastroenterol. 22:1 (1952). 4. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydergine in dogs, J. Pharmacol. & Exper. Therap. 111:329 (1954). 5. Browne, D. C. and Sparks, R.: Vomiting mechanisms: a clinical study of thiethylperazine, South. M.J., 54:(Sept.) 1961. 6. Browne, D. C. and Sparks, R. D.: Nausea and vomiting, study of thiethylperazine, Scientific Exhibit, American Medical Association Clinical Meeting, Washington, D.C., Nov. 28 (1960). 7. Maritano, M., Guerrieri, S., Menesini, R.: Prophylaxis and therapy of vomiting, Minerva anest. 26:343 (1960). 8. Modell, W.: Drugs of choice 1960-1961, C. V. Mosby Co., St. Louis, 1960, p. 339.

SANDOZ — ORIGINAL RESEARCH SERVING THE PHYSICIAN

acts on the True Vomiting Center

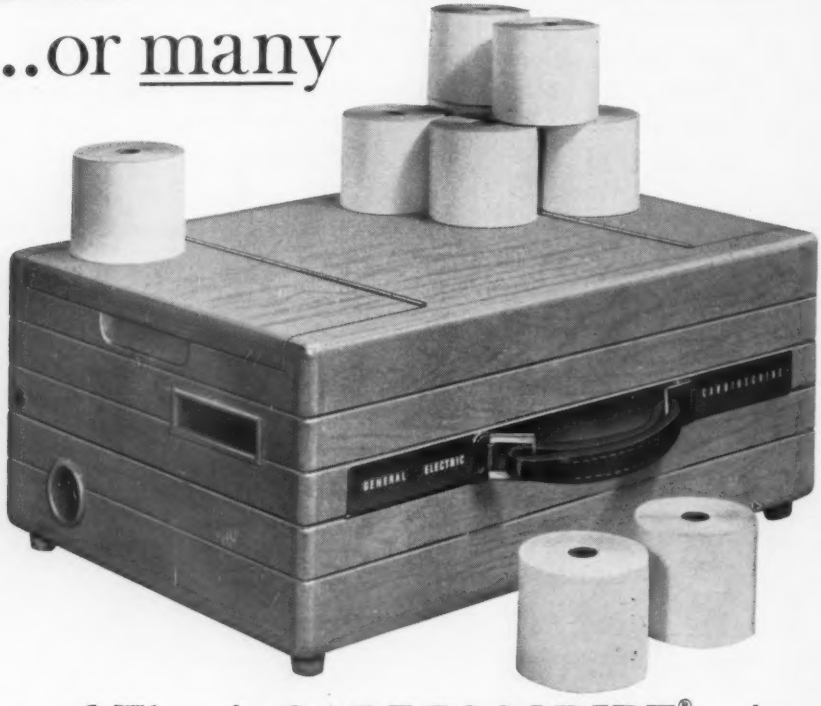
TORECAN®

Thiethylperazine Maleate

2-ethyl-mercapto-10-[3'-(1''-methyl-piperazinyl-4'')-propyl-1'] phenothiazine dimaleate

Whether you use

One EKG roll a week ...or many



General Electric CARDIOSCRIBE® writes a day-in, day-out record of reliability!

Whatever volume of electrocardiograms you handle, clarity and stability of tracings are *paramount considerations.*

CARDIOSCRIBE users take dependability for granted. This practical portable offers *proven* electronic fidelity . . . weds it to the most satisfactory direct-writing method ever devised. Precision-ground, hot-ribbon stylus cuts a razor-sharp waveform over its *entire excursion;* utilizes easy-to-handle, thermally sensitive paper.

Once your patient is "prepped," up to 30 leads can be made without shifting electrodes, even a full series of chest leads. There's much more too: swing-out paper drive for fast loading. Full 50-mm standard tape, allowing full-scale recording.

Contact your G-E x-ray representative for a first-hand demonstration soon. Or just write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub M-95.

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GENERAL ELECTRIC

for effective progestational therapy—by mouth

NORLUTIN

(norethindrone, Parke-Davis)

potent oral progestational agent



When given in small, oral doses, NORLUTIN has shown itself capable of producing clinical results comparable to those of parenterally administered progesterone and has therefore proved valuable in many hormonal disorders of menstruation and pregnancy. Therapeutic efficacy in such cases may be attributed to the capacity of NORLUTIN for restoration of estrogen-progesterone balance. Through its more convenient route of administration, NORLUTIN also enhances patient co-operation . . . helps to maintain a more stable regimen.

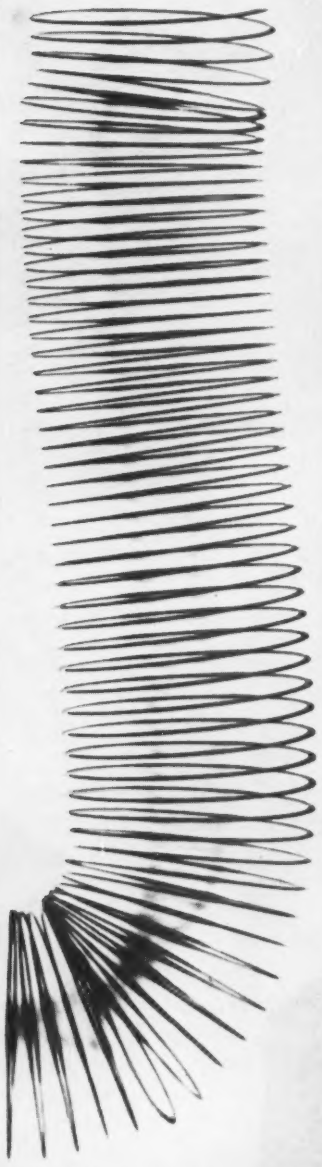
NORLUTIN (norethindrone, Parke-Davis), 17-alpha-ethinyl-19-nortestosterone, 5-mg. scored tablets. ***Indications:*** Progestational deficiencies. ***Dosage*** (assuming 28-day cycle): Amenorrhea, menstrual irregularity, functional uterine bleeding, infertility—5–20 mg. daily starting the fifth day of the cycle, ending the twenty-third day. Allow five days for withdrawal bleeding to occur. Habitual abortion—5 mg. twice daily on positive pregnancy test, through thirty-eighth week. Threatened abortion—20 mg. twice daily for five days, then 5 mg. twice daily through thirty-eighth week. Premenstrual tension, dysmenorrhea—10 mg. once or twice daily starting in pre-ovulatory phase, ending with the twentieth to the twenty-third day. Endometriosis—Treatment extends 6 to 9 months. Initially give 10 mg. daily for 2 weeks, increased by 10 mg. every 2 weeks up to 20 to 30 mg. daily. Pregnancy test—10 mg. daily for 3 days in nonpregnant women will produce withdrawal bleeding within 2 to 4 days after cessation of therapy. ***Precautions:*** Masculinization of the female fetus has been reported. Other side effects such as transient lethargy and nausea have also been reported. Spotting before calculated onset may indicate insufficient dosage. Development of hirsutism, change of voice, and acne have been reported as side effects. ***Supplied:*** 5-mg. scored tablets, bottles of 30.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

AN AMES CLINIQUICK®
CLINICAL BRIEFS FOR MODERN PRACTICE

the diabetic with proteinuria!



Protein in the diabetic patient's urine is usually cause for concern to the physician. He begins to think in terms of renal damage. This generally calls for a re-evaluation of the patient's diabetic state; in particular, his degree of diabetic control. Loss of control is a major factor in the development of degenerative nephropathy.

However, in the diabetic patient, proteinuria also may be indicative of disorders unrelated to the diabetic state. *Postrenal* disturbances such as lithiasis, cystitis, pyelitis, bilharziasis or prostatic impairment may produce protein in the urine. *Renal* proteinuria may be due to predisposing factors such as abscess, carbuncle or gangrene. These are usually of a transitory nature. When diabetes is the only apparent contributing factor to the presence of persistent proteinuria ("diabetic proteinuria"), renal damage associated with degenerative diabetic nephropathy is usually indicated.*

*Nagy El Mahallawy, M., and Sabour, M. S.: J.A.M.A. *173*:1783 (Aug. 20) 1960.

One of the simplest and most reliable means of evaluating the diabetic is through daily urine testing with URISTIX® for both *glucose* and *protein*—to indicate diabetic control, and forewarn of possible renal damage. Following a simple "dip-and-read" technique, URISTIX provides these *two* important test results *in just ten seconds*. Thus, it eliminates delay, guesswork, and fussing with equipment...making it equally valuable for office diagnosis or home testing.

to facilitate diabetic evaluation...

URISTIX®

BRAND *Reagent Strips*

colorimetric "dip-and-read" combination test for both *proteinuria* and *glucosuria*

- 1 dip...10 seconds...2 readings
- standardized color chart for dependable estimations
- unaffected by turbidity, drug metabolites, non-glucose reducing substances

available: URISTIX Reagent Strips, bottles of 125.

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This arthritic patient felt much better on Dianabol®

Mrs. K. S., 73, complained of severe pain in lower back. Diagnosis: osteo-arthritis and osteoporosis. Steroids and analgesics gave only moderate relief. Gradual weight loss continued. Dianabol, 10 mg./day, started. "Within a week symptomatic improvement had begun." Patient gained strength, agility, and sense of well-being. Photograph used with patient's permission.

Please turn page

Why arthritic patients feel much better on Dianabol

1. In arthritis, Dianabol improves general physical condition

Arthritis, like other chronic illnesses, plunges the body into a catabolic state. Protein stores are depleted; appetite wanes; weight drops; strength and vigor decline. By aiding the deposition, synthesis and utilization of protein, and by conserving calcium, Dianabol promotes lean weight gain, increases strength and vitality, and strengthens bone structure in patients with a wide range of chronic diseases. Recent studies show that adjunctive use of Dianabol may be particularly valuable in patients with arthritis to improve over-all clinical status. Kuzell and Naugler,[1] for example, report that arthritic patients on Dianabol "generally have experienced an increase in appetite, weight, strength and endurance." Kuzell and Naugler note further: "Unlike some other testosterone derivatives, the use of this compound [Dianabol] is not followed by virilizing phenomena. Fluid retention has been no problem."

2. In arthritis, Dianabol helps restore a sense of well-being

Plagued by pain and reduced mobility, arthritics often lose hope and become depressed. The marked improvement in general health usually associated with therapy with Dianabol may have a favorable effect in these patients, as it has in so many chronically ill individuals. As physical status improves, hope is revived and a sense of well-being restored. Commenting on the use of Dianabol in a group of debilitated, cachectic patients, Gingrich[2] states: "The majority of patients experienced increase in appetite and a feeling of well-being."

3. In arthritis, Dianabol augments the beneficial effects of salicylates, corticosteroids, etc.

Several investigators[1,3,4] have observed improved therapeutic response after the addition of Dianabol to antiarthritis regimens. Kuzell and Naugler[1] state: "In generalized osteoarthritis, symptoms have been less bothersome, and in ankylosing spondylitis gain in weight and strength has followed the use of Dianabol." Clark,[3] reporting on 12 hospitalized patients with rheumatoid arthritis being given moderate to large doses of corticosteroids with evidence of steroid intoxication, noted that the addition of Dianabol promptly decreased joint symptoms but increased steroid intoxication. However, with Dianabol it was possible to reduce corticosteroid dosage considerably, while maintaining and even furthering clinical improvement. In 15 ambulatory patients on small maintenance doses of corticosteroids, the addition of Dianabol resulted in further clinical improvement which was continued even when corticosteroid dosage was reduced in some cases.[3,4]

4. In arthritis, Dianabol counteracts the catabolic effects of corticosteroids

Prolonged use of corticosteroids may result in excessive breakdown of protein in all tissues, including bone,[5] as well as undue phosphorus and calcium loss.[6] If protein destruction is allowed to go unchecked, it may lead to osteoporosis—a condition that has occurred with increasing frequency in patients receiving corticosteroids for extended periods.[7]

Tillis[5] asserts that it is "imperative" to restore the protein bone matrix in such patients

through the use of an anabolic agent. He studied the specific anabolic benefits of Dianabol in 50 patients with osteoporosis (34 postmenopausal and 16 corticosteroid-induced), most of whom also had rheumatoid arthritis. Dianabol relieved bone pain, increased strength and vigor, and induced a sense of well-being in 41 (82 per cent) of these patients. Edema, observed in 8 patients, was cleared in 4 by reduction of dosage; the remaining 4 responded promptly to hydrochlorothiazide. Gastric distress was noted in 2 patients, slight hoarseness in 1 woman, and facial acne in 1 woman. Other investigators[8,9] have shown that addition of Dianabol to the regimens of patients receiving corticosteroids improved nitrogen and potassium metabolism and reduced phosphorus and calcium losses. Reporting on 10 patients taking corticosteroids, most of whom had corticosteroid-induced osteoporosis and/or myopathy, Abbott[9] states: "In the patients who showed a markedly negative nitrogen balance the administration of 10 mg. of Dianabol per day greatly reduced the protein deficit. In others who were eating well and taking smaller amounts of corticosteroids a positive nitrogen balance resulted which increased with Dianabol." Abbott notes that creatinuria, which occurred on corticosteroids alone, was increased by Dianabol, as it is by methyltestosterone and the newer oral methyl- or ethyl-testosterone derivatives. However, he observes that the "significance of this creatinuria is not known and no ill effects have been ascribed to this change." While the finding of elevated serum aldolase levels raised the theoretical possibility of potentially deleterious effects, Vignos *et al*[8] and Abbott[9] noted no androgenic or myopathic effects and no liver disorders in patients who took Dianabol and corticosteroids for up to 8 months. Kuzell and Naugler[1] state it is their impression that Dianabol has checked weight loss following prolonged administration of triamcinolone in patients with rheumatoid arthritis. They add that, with Dianabol, protein patterns have migrated toward normal profiles, purpura consequent to corticosteroid administration has been lessened, and the erythrocyte sedimentation rate has been diminished.

REFERENCES: 1. Kuzell, W. C., and Naugler, W. E.: Paper presented at the Annual Meeting of the American Rheumatism Association, Hollywood-By-The-Sea, Florida, June 9-11, 1960. 2. Gingrich, G. W.: Clinical report to CIBA. 3. Clark, G. M.: Paper presented at the Seventh Interim Session of the American Rheumatism Association, Dallas, Texas, Dec. 10, 1960. 4. Clark, G. M., Kaplan, S., Goobar, J., and Mills, D.: Arthritis and Rheumatism *4*:106 (Feb.) 1961. 5. Tillis, H. H.: Clin. Med. *8*:274 (Feb.) 1961. 6. Lockie, L. M.: J.A.M.A. *170*:1063 (June 27) 1959. 7. Boland, E. W.: J.A.M.A. *150*:1281 (Nov. 29) 1952. 8. Vignos, P. J., Jr., Abbott, W. E., Post, R. S., and Levy, S.: J. Lab. & Clin. Med. *56*:954 (Dec.) 1960. 9. Abbott, W. E.: Research report to CIBA. 10. Misurale, F.: Minerva med. *51*:996 (March 21) 1960.

advantages of Dianabol over other anabolic agents as an adjunct in the treatment of arthritis

▪ *Dianabol has an exceptionally favorable anabolic/androgenic ratio.* The anabolic effects of Dianabol occur at dosages which generally preclude androgenic side reactions. In this respect, Dianabol has proved superior to 12 other anabolic compounds.[10] Laboratory evidence also indicates that Dianabol has no estrogenic, progestational, or corticoid-like activity which might be clinically detrimental.
▪ *Dianabol is economical.* Low in cost, Dianabol is especially suitable for arthritic patients who usually require long-term therapy.
▪ *Dianabol is effective orally.* Because it is an oral preparation, Dianabol spares patients the inconvenience and discomfort of parenteral drugs.

Dianabol®

low-cost, oral anabolic agent

an important new ally in the treatment of arthritis

Other indications for Dianabol:
• Underweight, debility and weakness
• General physical weakness and cachexia due to chronic diseases
• Retarded convalescence from illness, surgery, fractures, wounds, and burns

For complete information about Dianabol (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N. J.

SUPPLIED: *Tablets*, 5 mg. (pink, scored); bottles of 100.

DIANABOL® (methandrostenolone CIBA)

CIBA
SUMMIT, NEW JERSEY

2/2954MB

MORE SECURITY IN POSTCORONARY YEARS

DANILONE®

(Phenindione, Schieffelin)

A "MAXIMUM SECURITY" ANTICOAGULANT

FAST, PRECISE ADJUSTMENT OF PROTHROMBIN LEVEL

After recovery from a myocardial infarction, DANILONE—a "maximum security" anticoagulant—guards the patient against the inevitable[1] subsequent recurrence with less risk of hemorrhage. **DANILONE has a short latent period and a short recovery period, and therefore, noncumulative action.** Thus, the prothrombin level may be rapidly and accurately adjusted upward or downward by simple alteration of oral dosage. DANILONE may be administered to many patients with shock, debilitation, hepatic, renal or gastrointestinal disease. The practical advantages of DANILONE are well documented.

EARLY ONSET "...fast in reaching therapeutic levels..."[2]

FAST DISSIPATION "...rapid return to a normal level in the event of undue prolongation of prothrombin time or hemorrhage."[3] (After withdrawal of DANILONE, the return to normal range of prothrombin time is well advanced in 24 hours, complete in 40 hours.)

RECORD OF SAFETY "...can be administered with reasonable safety in the presence of many conditions (other than that for which the anticoagulant is administered)..."[4]

The short latent period and rapid return to normal prothrombin blood levels when DANILONE is discontinued allow the physician to obtain even more satisfactory control by dividing the daily dose into two twelve-hour intervals.

"An advantage of a twelve-hour dosage schedule is that only half the daily dose may have been given when bleeding or excess prothrombin effect is discovered, allowing earlier adjustment of dosage or discontinuance."[4]

FEWER PROTHROMBIN DETERMINATIONS REQUIRED "...patients on long-term therapy can usually be...controlled with estimations at two- to four-week intervals,"[5] after initial adjustment period.

ECONOMICAL "...We have found phenindione inexpensive..."[3]

PREDICTABLE "...and relatively easy to manage with a reasonably constant daily dosage."[3]

Complete literature available on request to physicians for indications, dosages and precautions.

Supplied: In 50 mg. scored tablets, bottles of 100 and 1,000.

1. Manchester, B.: Ann. Int. Med. *47*:1202 (Dec.) 1957. 2. Harper, B.F., and Johnson, R.: J.M.A. Georgia *45*:149 (April) 1956. 3. Wood, J.L. *et al.*: J.A.M.A. *159*:635 (Oct.) 1955. 4. Sise, H. *et al.*: Am. Heart J. *53*:132 (Jan.) 1957. 5. Dewar, H.A.: Practitioner *186*:41 (Jan.) 1961.

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Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective



for the tense and nervous patient

1 simple dosage schedule relieves anxiety dependably – without the unknown dangers of "new and different" drugs

2 does not produce ataxia, stimulate the appetite or alter sexual function

3 no cumulative effects in long-term therapy

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*–400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
*TRADE-MARK

Miltown®
meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*

CM-4751



the first complete physiologic regulator of female cyclic function

ENOVID®

(BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER)

The basic action

ENOVID closely mimics the balanced progestational-estrogenic action of the functioning corpus luteum. This action is readily understood by a simple comparison. In effect, ENOVID *induces a physiologic state which simulates early pregnancy—except that there is no placenta or fetus.* Thus, as in pregnancy, the production or release of pituitary gonadotropin is inhibited and ovulation suspended; a pseudodecidual endometrium ("pseudo" because neither placenta nor fetus is present) is induced and maintained. Further, during ENOVID therapy, certain symptoms typical of normal pregnancy may be noted in some patients, such as nausea—which is usually mild and disappears spontaneously within a few days—breast engorgement, some degree of fluid retention, and often a marked sense of well-being. There is no androgenicity. ENOVID *is as safe as the normal state of pregnancy.*

The basic applications

1. Correction of menstrual dysfunction. *Cyclic* therapy with ENOVID controls dysfunctional uterine bleeding (menorrhagia, metrorrhagia) and often establishes a normal menstrual cycle in amenorrhea.

2. Ovulation suppression (to suspend fertility). For this purpose ENOVID is administered *cyclically*, beginning on day 5 through day 24 (20 daily doses). The ovary remains in a state of physiologic rest and there is no impairment of subsequent fertility. Continuous administration for more than two years is not recommended.

3. Postponement of the menses for reasons of health (impending hospitalization for surgery, during treatment of Bartholin's gland cysts, acute urethritis, rectal abscess, trichomonal or monilial vaginitis), travel, forthcoming marriage, or pressing business or professional engagements. For this purpose ENOVID may be started at any time in the cycle up to one week before expected menstruation. Upon discontinuation, normal cyclic bleeding occurs in three to five days.

4. Threatened abortion. *Continuous* ENOVID treatment provides balanced hormonal support for the endometrium in threatened or habitual abortion.

5. Endocrine infertility. ENOVID has been used successfully in *cyclic* therapy of endocrine infertility, promoting subsequent pregnancy through a probable "rebound" phenomenon.

6. Endometriosis. *Continuous* therapy with ENOVID corrects endometriosis by producing a pseudodecidual reaction with subsequent absorption of aberrant endometrial tissue.

The basic dosage

Basic dosage of ENOVID is 5 mg. daily in *cyclic* therapy, beginning on day 5 through day 24 (20 daily doses). Higher doses may be used with complete safety to prevent or control occasional "spotting" or breakthrough bleeding during ENOVID therapy, or for rapid effect in emergency treatment of dysfunctional bleeding and threatened abortion. ENOVID is available in tablets of 5 mg. and 10 mg. Literature and references, covering over five years of intensive clinical study, available on request.

SEARLE *Research in the Service of Medicine*

...*unfettered*

From the beginning, woman has been a vassal to the temporal demands—and frequently the aberrations—of the cyclic mechanism of her reproductive system. Now, to a degree heretofore unknown, she is permitted normalization, enhancement, or suspension of cyclic function and procreative potential. This new physiologic control is symbolized in an illustration borrowed from ancient Greek mythology—Andromeda freed from her chains.

One daily dose controls edema and hypertension around the clock

Every tablet delivers 24 hours' continuous thiazide action

ENDURON

Trademark

(Methyclothiazide, Abbott) Supplied in 2.5 and 5 mg. grooved tablets.

Enduron provides you the most sustained therapeutic effect of any thiazide available. Diuretic response is smooth and continuous. Even at end of the 24 hours, patients are still eliminating excess sodium well above control amounts.[1]

This unique duration permits convenient *once*-daily dosage—and without resulting gaps in the action. Easy for you to supervise, convenient for your patient—and fewer forgotten doses.

POTASSIUM CONTROL SIMPLIFIED

Potassium depletion is rare. Enduron's *single* daily dose causes but a *single* temporary peak of potassium loss.

Moreover, Enduron's effect on potassium has upper limits. Thus doubling the single dose from 5 to 10 mg. approximately doubles the output of sodium; yet under this same condition, potassium output increases little or not at all.[2]

Use Enduron to treat the edema of congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, or steroid therapy. Enduron also demonstrates significant antihypertensive effect.[1,3] You may use it as a primary measure for mild to moderate hypertension, or as an adjunct in more severe cases.

1. Ford, R. V. Current Therap. Res., 2:422-430, Sept., 1960.
2. Fuchs, Morton, and Seller, Robert H., to be published.
3. Bryant, J. M., et al., Current Therap. Res., 3:1-4, Jan., 1961.

ABBOTT

10B224





Where blood pressure climbs
—keep it under control with
Enduronyl

Announcing a once-a-day thiazide/rauwolfia antihypertensive

ENDURONYL

Trademark

(Methyclothiazide and Deserpidine, Abbott) (ENDURON™ and HARMONYL®)

Yes, just *once* daily is the dose for hypertension. Blood pressure starts down steadily: improvement usually is substantial within 10 days. Further reduction may continue over following weeks. At the same time, excess sodium and water are consistently eliminated.

Giving Enduronyl just once a day means fewer forgotten doses. A smoothly sustained therapeutic response, too.

On the other hand, single doses produce only one low, brief peak of potassium excretion. Hence one-a-day dosage means reduced chance of potassium depletion, since there's but one daily boost to the patient's potassium outgo.

WHAT IS ENDURONYL?

Enduronyl combines two well-established antihypertensive agents: (1) Enduron, Abbott's long-acting thiazide diuretic, and (2) Harmonyl, a rauwolfia derivative of low side effects. Together they provide greater hypotensive action than with either alone.

Enduronyl is supplied in two formulas, to cover a wide range of cases from mild to moderately severe hypertension. Would you like the literature? Write Abbott, North Chicago, Ill.

Supplied:
Enduronyl—(5 mg. Enduron, and 0.25 mg. Harmonyl)
Enduronyl Forte—(5 mg. Enduron, and 0.5 mg. Harmonyl)

ABBOTT

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HY-0984

Hygroton®

brand of chlorthalidone

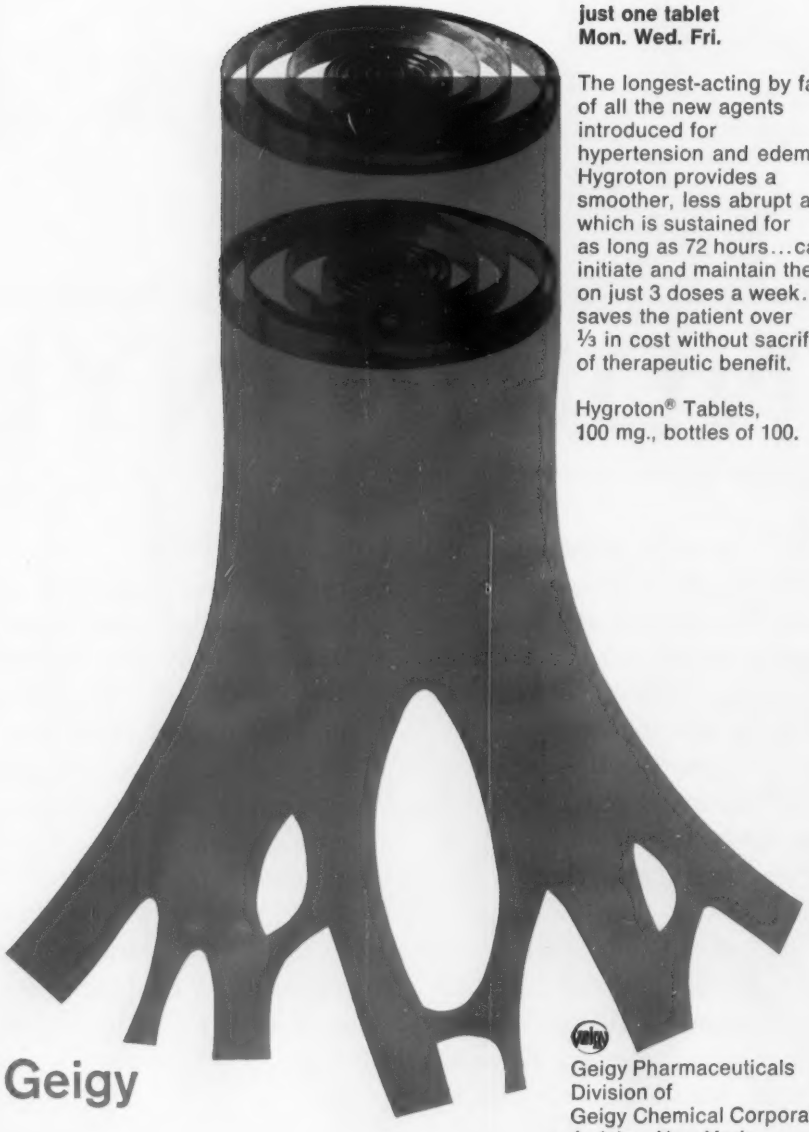
in hypertension and edema

17 days free each month from drug administration

just one tablet Mon. Wed. Fri.

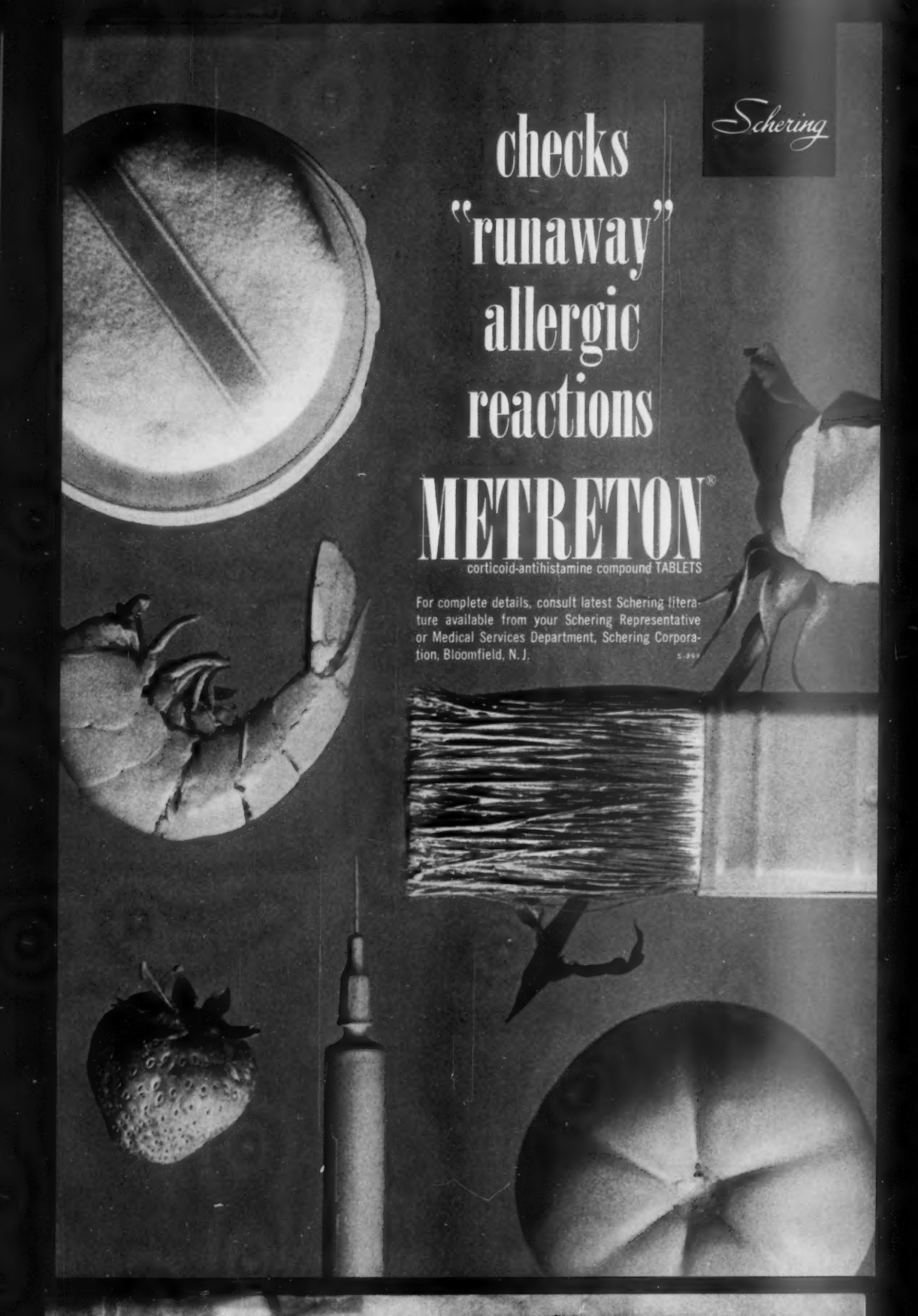
The longest-acting by far of all the new agents introduced for hypertension and edema, Hygroton provides a smoother, less abrupt action which is sustained for as long as 72 hours...can initiate and maintain therapy on just 3 doses a week... saves the patient over ⅓ in cost without sacrifice of therapeutic benefit.

Hygroton® Tablets, 100 mg., bottles of 100.



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Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York


Schering
checks
"runaway"
allergic
reactions
METRETON®
corticoid-antihistamine compound TABLETS
For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.
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in its service to children who need remedial education? It furnishes —

1. Group living and learning experience with others of a similar aptitude and level of development.

2. The functioning of a multidisciplinary team with long experience in evaluating potential and in structuring programs in a residential setting unique in its wide range of homogeneous groupings.

3. A philosophy of optimum blending of traditional methods with the best of the new from the frontiers of research.

4. Established programs of diagnosis, treatment, research, and training soundly based on the wide spectrum of a multidisciplinary team of experts.

Serving the East Coast, Devereux Schools are located at Devon, Pennsylvania (Mr. Charles J. Fowler, Director of Admissions); serving the West Coast, Devereux Schools at Santa Barbara, California (Mr. Keith A. Seaton, Registrar); and serving the Southwest, Devereux Schools at Victoria, Texas (Mr. John M. Barclay, Director of Development). Your inquiries are welcomed.

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Devon, Pennsylvania
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IN BRIEF

ATARAXOID contains the glucocorticoid prednisolone and the ataractic agent, hydroxyzine.

ADVANTAGES: ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-inflammatory action of prednisolone, a well-established corticosteroid, for superior control of the signs and symptoms of rheumatoid arthritis without *unexpected* side effects. An important result of the therapeutic effects of ATARAXOID is noted by Warter*: "In addition it was possible in many cases for the first time to gain the active cooperation of patients in the management of their disease."

INDICATIONS: Rheumatoid arthritis; other collagen diseases and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); allergic states, including chronic bronchial asthma and severe hay fever; and allergic/inflammatory diseases of the skin and eyes.

ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 ATARAXOID *5.0* Tablets. *Maintenance*—1-4 ATARAXOID *5.0* Tablets or 2-8 ATARAXOID *2.5* Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

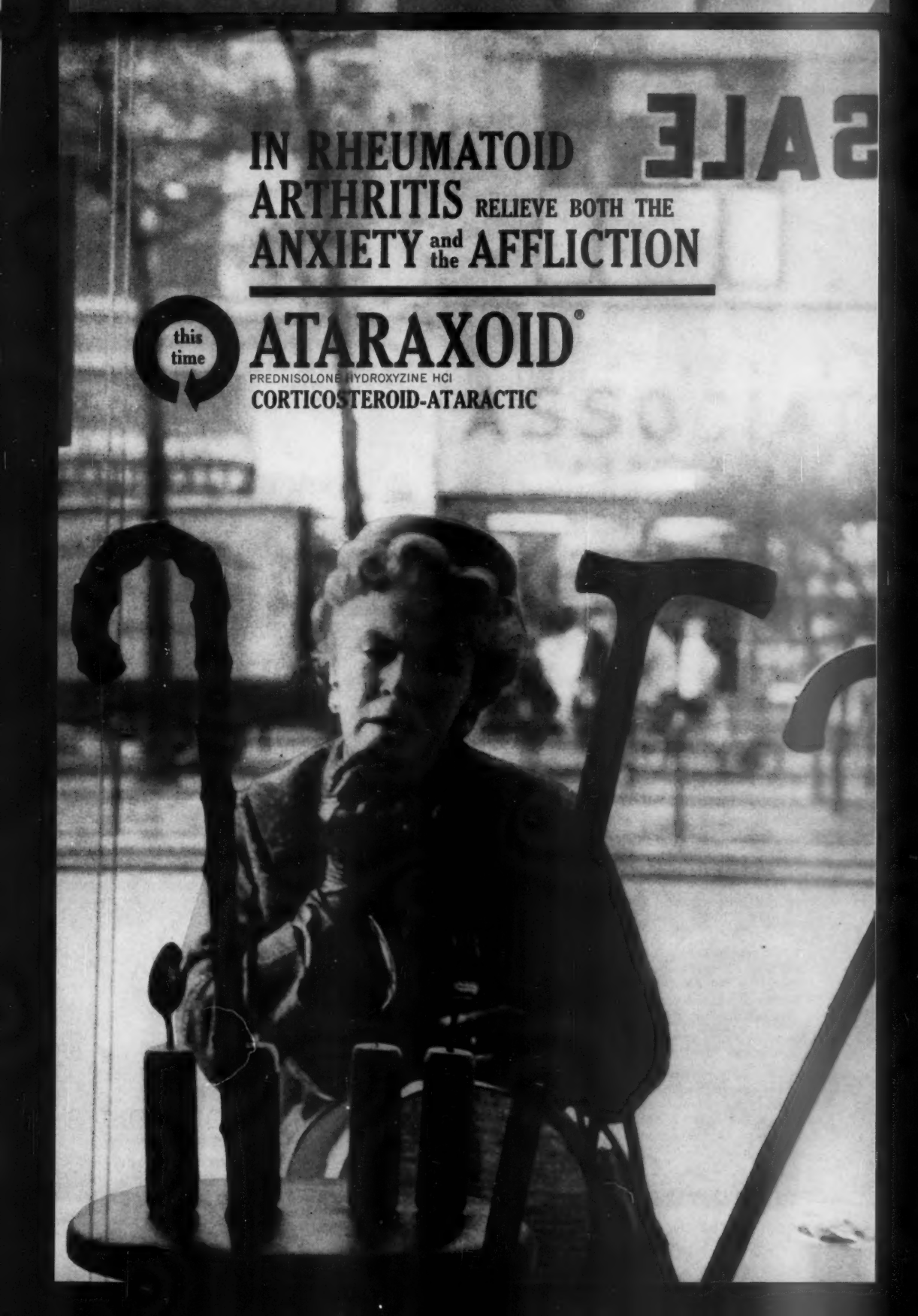
SUPPLIED: As green, scored ATARAXOID *5.0* Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID *2.5* Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.

*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J.M. Soc. New Jersey 54:7, 1957.

Pfizer Science for the world's well-being™

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Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York


IN RHEUMATOID ARTHRITIS RELIEVE BOTH THE ANXIETY and the AFFLICTION
this time
ATARAXOID®
PREDNISOLONE HYDROXYZINE HCl
CORTICOSTEROID-ATARACTIC



DUAL ACTION IN HEPATIC COMA

ARGININE MONOHYDROCHLORIDE

R-gene®

CUTTER

REDUCES HIGH BLOOD AMMONIA LEVELS... HELPS OVERCOME THE ACCOMPANYING ALKALOSIS

R-gene can be used to prevent impending hepatic coma and has dramatically increased the survival rate in patients in deep coma where the mortality rate is normally extremely high.[1] It provides arginine to detoxify circulating blood ammonia by accelerating its conversion to urea in the liver.[1-3] In addition, R-gene supplies chloride which combines with excess sodium to overcome the alkalosis induced by vomiting which usually accompanies ammonia intoxication.[4]

Because of this dual action, R-gene is of potential benefit in all cases where elevated ammonia levels exert a toxic effect as in hepatic coma, ammonia intoxication due to ingestion of ammonium salts, acute hepatic insufficiency, and following massive upper gastrointestinal hemorrhage.

The R-gene package consists of a half liter Saftiflask® containing 400 cc. of a 5% solution of L-arginine monohydrochloride, a 100 cc. Ambot® of 50% dextrose,* and administration set. Each 100 cc. of R-gene contains: L-arginine monohydrochloride 5.0 Gm., nonpyrogenic distilled water q.s.

*Administration of dextrose in conjunction with arginine appears to aid the total ammonia utilization.

For maximum effectiveness, measures to reduce ammonia intake should be started with R-gene administration including reduction or withdrawal of protein intake, control of gastrointestinal bleeding, prompt removal of blood from the intestine, supression of ammonia production in the intestine with large oral doses (4-12 Gm. daily) of neomycin.[3,5]

1. Najarian, J. S., *et al.*: Am. J. Surg. *96*:172, 1958. 2. Wolfe, S. J., *et al.*: cited by Fast, B. B., Arch. Int. Med. *10*:467, 1958. 3. Editorial, New England J. M. *259*:1181, 1958. 4. Editorial, J.A.M.A. *169*:1076, 1959. 5. Britton, R. C.: Connecticut M. J. *22*:537, 1958.

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Full information available from your Cutter man, or write to Dept. 1-18J

Here are eight good reasons why you should write "Raudixin" in the treatment of high blood pressure:



1. Rigorous pharmacognostic examinations eliminate substandard Rauwolfia species and establish uniformity of the product.



2. The whole root, including all its active fractions, is used for maximal antihypertensive activity with minimal sedation.



3. Radioisotope dilution assay (important, but rarely done elsewhere) determines potency.



4. Biological assay measures the ability to counteract the pressor effect of standard doses of epinephrine in the dog.



5. Biological assay measures the ability to produce ptosis in the mouse in comparison with a reference standard.



6. Safety verified by toxicity tests.



7. Chemical assay establishes the active alkaloid content.



8. Every Raudixin tablet to reach your patient meets the high Squibb standards for effectiveness, potency and uniformity.

For full information, see your Squibb Product Reference or Product Brief.

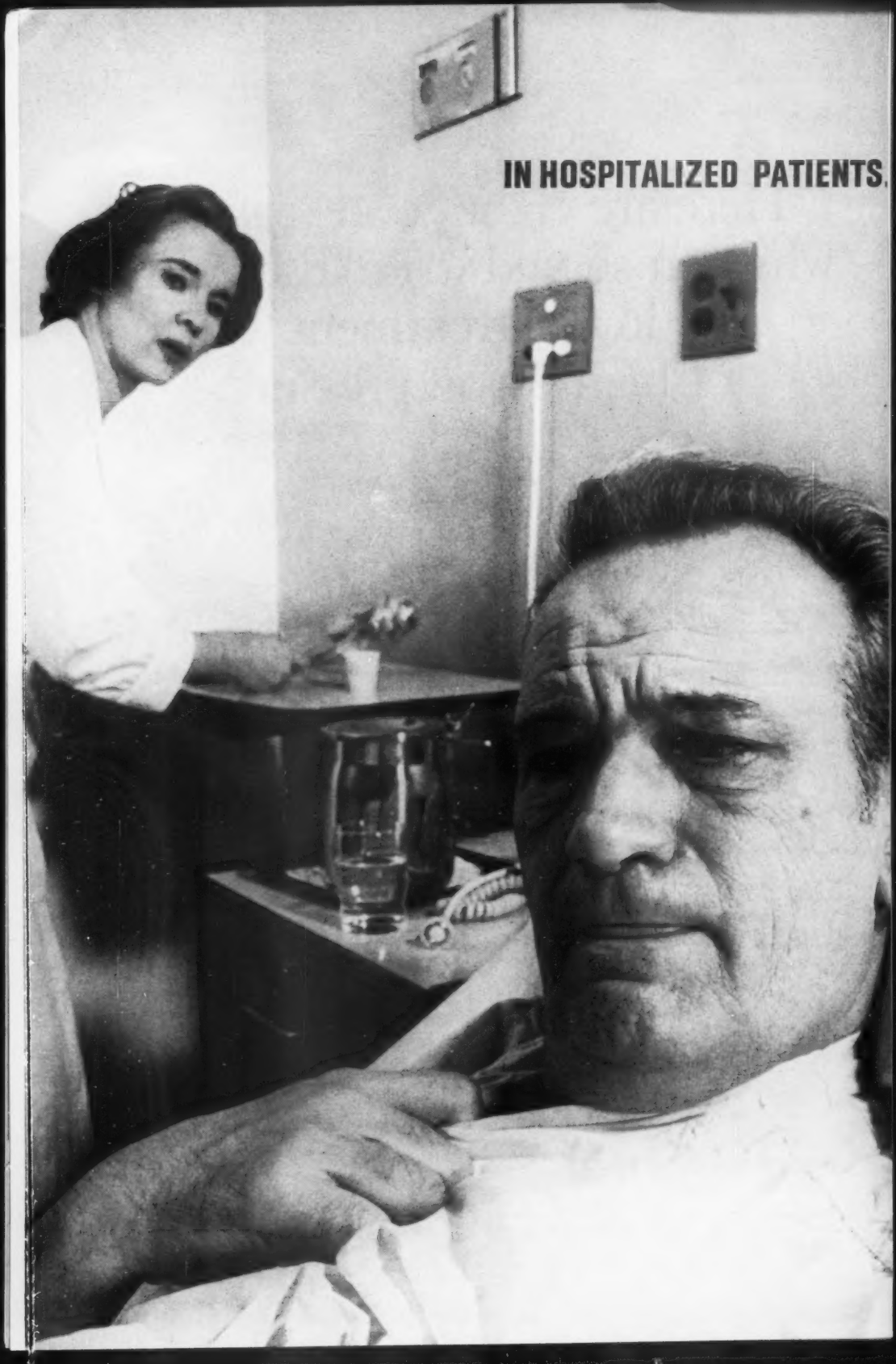
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Squibb Standardized Whole Root Rauwolfia Serpentina

Supply: 50 mg. and 100 mg. tablets 'Raudixin'® is a Squibb trademark.


IN HOSPITALIZED PATIENTS.

Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

and "screens out" certain side effects of tranquilizers, making it virtually free of:



"The value of the phenothiazines as tranquilizers has been established. [However] many distressing side effects have been reported with these drugs.... Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines."[1]

In Agitated Medical/Surgical Patients—"A new phenothiazine derivative, thioridazine [Mellaril], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions.... The response to treatment was considered satisfactory in 83.4 per cent of patients.... In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."[2]

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d.

Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient, A.M. & C.T. 7:364 (June) 1960.

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SANDOZ

in the wide middle region of pain



Percodan®

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

TABLETS

fills the gap between mild oral and potent parenteral analgesics[1-7]

- acts in 5-15 minutes
- relief usually lasts 6 hours or longer
- toleration excellent... constipation rare
- sleep uninterrupted by pain

Each Percodan* Tablet contains 4.50 mg. dihydrohydroxycodeinone HCl, 0.38 mg. dihydrohydroxycodeinone terephthalate (warning: may be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

for fast and thorough pain relief

AVERAGE ADULT DOSE
1 tablet every 6 hours; may be habit-forming. Federal law permits oral prescription.

Also Available
For greater flexibility in dosage—Percodan®-Demi: The complete Percodan formula, but with only half the amount of salts of dihydrohydroxycodeinone and homatropine.

1. Blank, P., and Boas, H.: Improved analgesia for moderate pain, Ann. West. Med. & Surg. 6:378, 1952. 2. Bonica, J. J., et al.: The management of postpartum pain with dihydrohydroxycodeinone (Percodan): Evaluation with codeine and placebo, West. J. Surg. 65:84, 1957. 3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief, M. Times 84:1318, 1956. 4. Chasko, W. J.: Pain-free dental surgery: Postoperative extension of the pain-free state, J. District of Columbia Dent. Soc. 31:3, No. 9, 1956. 5. Cozen, L.: Office Orthopedics, ed. 2, Philadelphia, Lea & Febiger, 1953, pp. 120, 138, 145, 156, 234. 6. Nicolson, W. P., Jr., and Skandalakis, J. E.: Control of postoperative pain, J.M.A. Georgia 46:471, 1957. 7. Piper, C. E., and Nicklas, F. W.: Percodan for pain in industrial practice, Indust. Med. 23:510, 1954; abstracted, Clin. Med. 1:1006, 1954, Current M. Digest 22:135, No. 3, 1955.

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For rapid response in acute agitation and hyperactivity, anxiety and phobia, hysteria and panic states, alcoholism and drug withdrawal reactions; or in severe emotional disturbances where oral administration is impractical—Librium Injectable.

In the 1001 emergency situations of daily practice and in the hospital emergency room when immediate calming is required for anxious, agitated, restless, confused, disoriented, obstreperous, protesting or panicky patients—Librium Injectable—in situations ranging from accident cases to tragic life events; from behavior crises to emotional crises; from alcoholic DT's and hallucinosis to drug withdrawal or postconvulsive reactions; from upsetting diagnostic procedures to pre- and postoperative states.

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Librium HCl Injectable is supplied in 100-mg ampuls for parenteral administration.

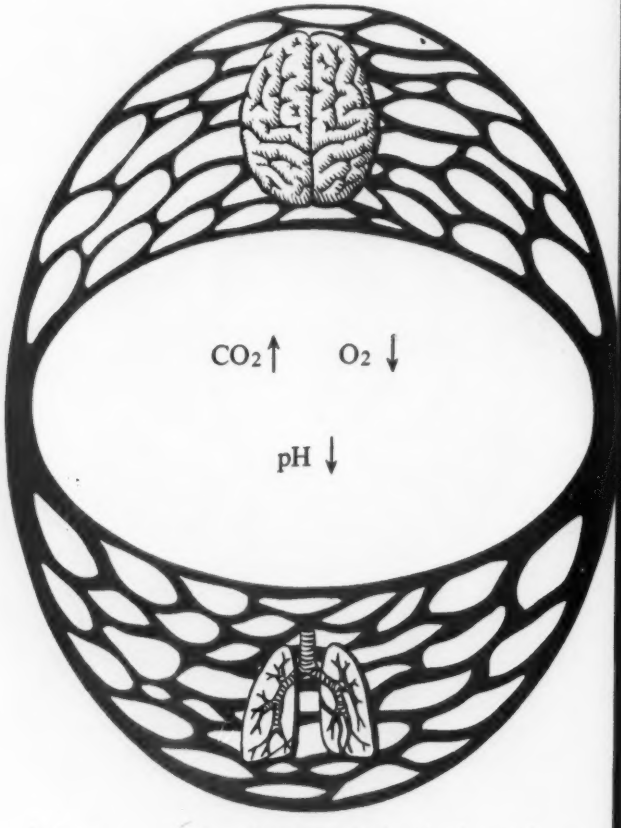
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LIBRIUM® Hydrochloride—7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride

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in respiratory diseas

a selective respiratory stimulant



before therapy

these patient-complaints...

fatigue
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mental confusion
irritability
personality changes
muscle weakness

in these clinical situations..

■ Frequent or refractory upper respirator infectious or allergic disorders ■ Chroni bronchitis ■ "Heavy smoker's syndrome ■ Geriatric respiratory involvement ■ Cardio-pulmonary disease (cor pulmonale ■ Chest cage abnormalities ■ Long expo sure to occupational irritants; smog

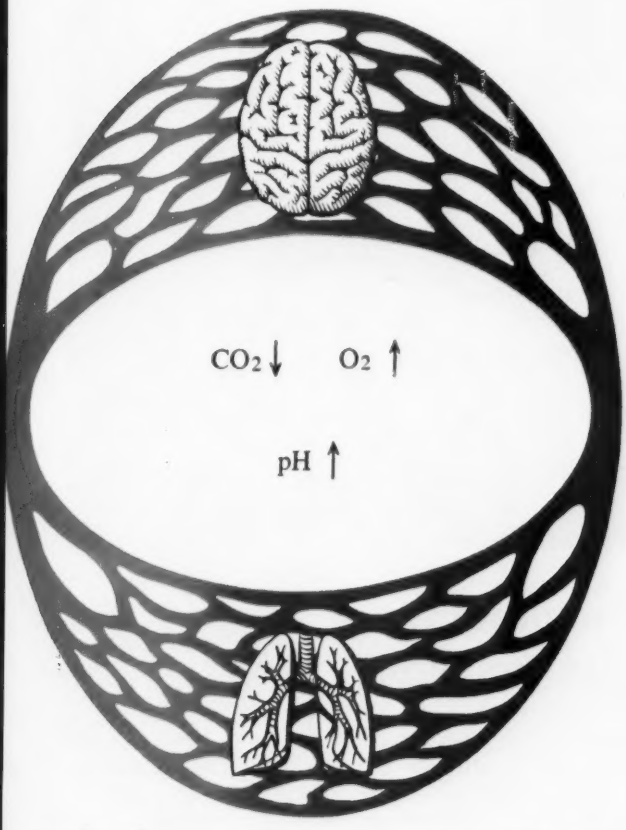
NOTE: EMIVAN VENTILATES. The effectiveness of EMIVAN is dependent upon a patent airway. Therefore, bronchodilators, corticosteroids, antimicrobials and wetting agents, and in severe cases, tracheal aspiration, if needed, should be employed as required to treat the underlying pulmonary disorder.

DOSAGE: To initiate therapy, 1 or 2 EMIVAN Tablets t.i.d. (Consult product brochure for complete dosage, administration, side effects, precautions and contraindications). ■ SUPPLIED: EMIVAN Tablets (uncoated providing 20 mg. vanillic diethylamide), bottles of 100 and 1,000.

NEW...EMIVAN® TABLETS

brand of ethamivan

or treatment of symptoms of CO_2 accumulation



with Emivan

may be the result of CO_2 accumulation...

Consider that their specific complaints may be the consequences of CO_2 retention *(hypercapnia)* and secondary reduced oxygen saturation *(hypoxia)* due to hypoventilation.

and can be alleviated safely with EMIVAN

EMIVAN selectively stimulates the medullary respiratory center to increase the *depth* of breathing and (to a lesser extent) the *rate* of breathing . . . *without* cardiovascular side effects, neurological damage, or secondary post-stimulatory depression.



For the emergency treatment of the comatose or severely depressed patient (when due to depressant overdosage or severe pulmonary involvement): *INTRAVENOUS EMIVAN, can be life-saving*



U.S. VITAMIN & PHARMACEUTICAL CORP.
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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

in severe drug and food sensitivity... rapid relief and control of symptoms on short-term therapy with Decadron®



Brief treatment with DECADRON – orally or parenterally – can provide rapid and effective control of allergic emergencies and acute allergic disorders such as reactions to foods, drugs, plants, weeds, and animals. In 40 patients given Injection DECADRON Phosphate, "subjective improvement was often noticed within one hour and objective improvement recorded within 4 hours."[1] Therapeutic doses of steroids may help prevent recurrences of severe allergic states, without interfering with desensitization or other immunity procedures.[2]

Before prescribing or administering DECADRON, the physician should consult the detailed information on use accompanying the package or available on request.

References: 1. Grater, W. C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. 6:(No. 3) 181, 1959.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000. As Injection DECADRON Phosphate in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt; inactive ingredients: 8 mg. creatinine, 10 mg. sodium citrate; sodium hydroxide to pH 7.8, and water for injection q. s. 1 cc.; preservatives: 0.32 per cent sodium bisulfite and 0.5 per cent phenol. DECADRON is a trademark of Merck & Co., Inc.

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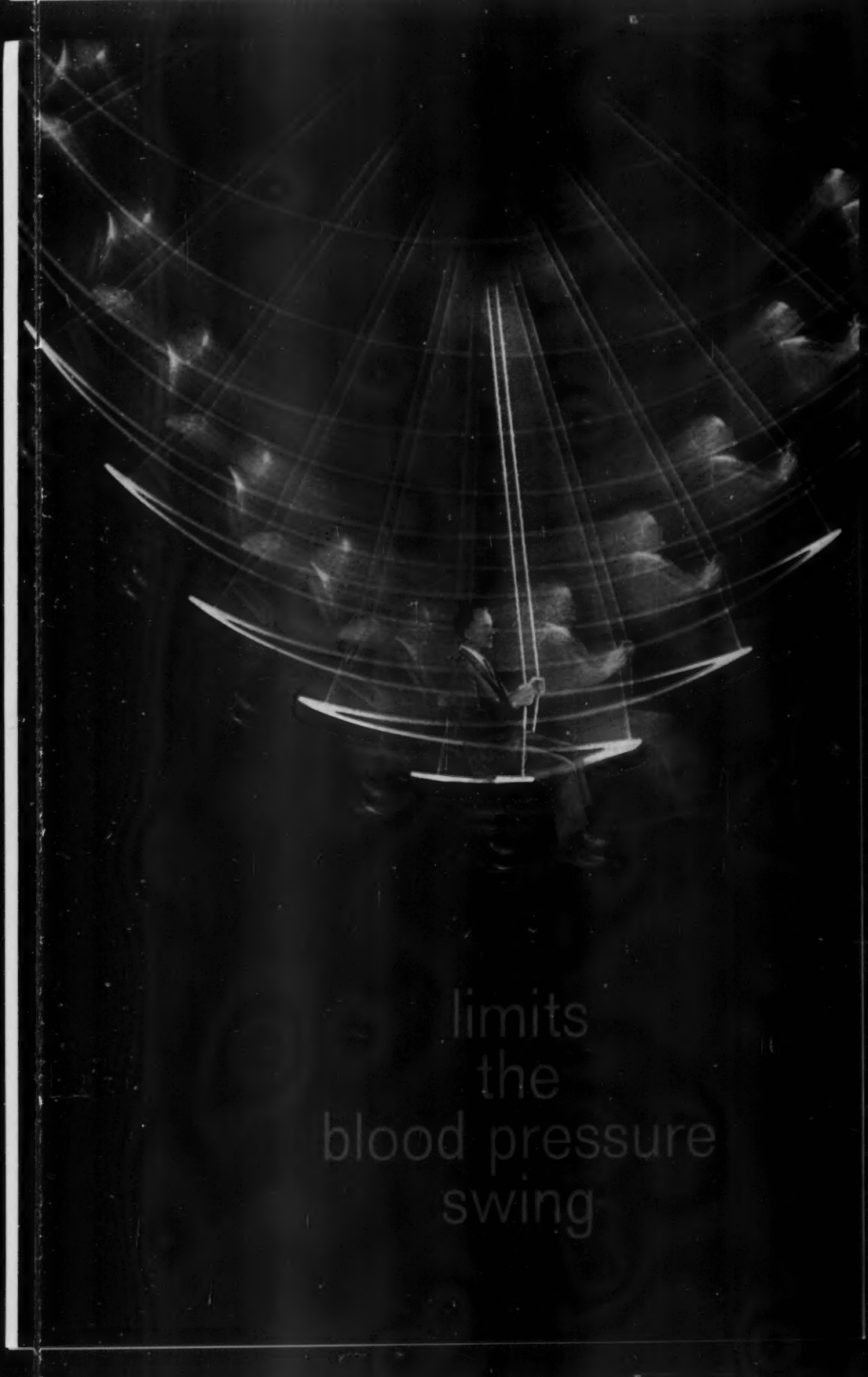
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Dexamethasone

TREATS MORE PATIENTS MORE EFFECTIVELY

DECADRON: Recommended dosage schedule in the treatment of drug and food sensitivity reactions

time	amount	administration
1st day	one to two cc. (4 to 8 mg.) Injection DECADRON Phosphate intramuscular	repeated as necessary (In substituting tablet therapy, give the first oral dose four or five hours before the final parenteral dose.)
2nd day	two 0.75 mg. Tablets DECADRON	b.i.d.
3rd day	two 0.75 mg. Tablets DECADRON	b.i.d.
4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
5th day	one 0.75 mg. Tablet DECADRON	per day
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7th day	RETURN VISIT	


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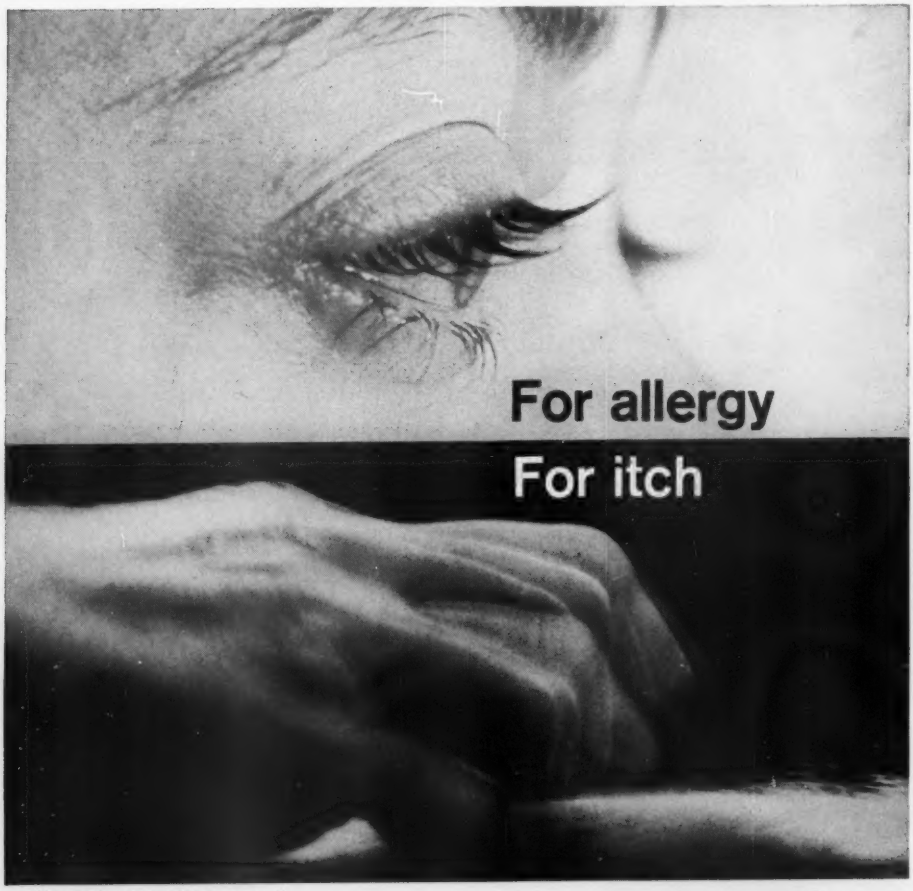
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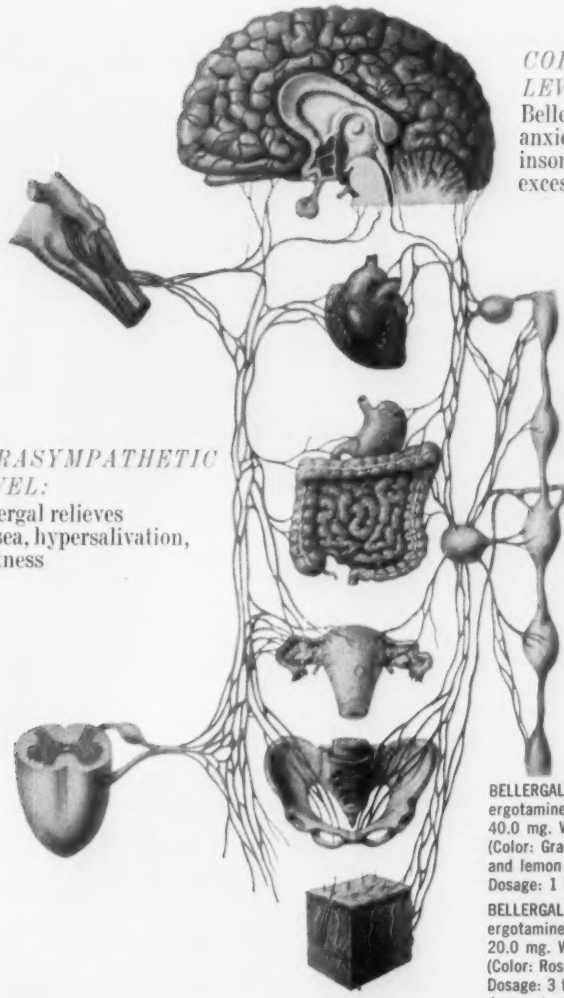
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Note: The degree of central nervous system depression induced by SPARINE has not been great; however, in the acutely inebriated person the initial dose should not exceed that recommended to be sure that the depressant effect of alcohol is not enhanced. SPARINE should not be used in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates, etc.). In patients with cerebral arteriosclerosis, coronary heart disease, or other conditions where a drop in blood pressure may be undesirable, SPARINE should be used with caution.

in acute behavior disorders

Fink and Vlavianos[2] reported that with SPARINE "*Violence* and *acute overactivity* were minimized, and combativeness was reduced. The patients became more co-operative." SPARINE did not impair mental acuity. Insomnia was reduced in all overactive patients. Patients with hallucinations or delusions generally improved as long as medication was continued. Acute hallucinations were quickly relieved. At the end of these studies of 200 ward patients: 37 were released; 41 were transferred to an open ward with privileges and were being considered for release. No side effects were observed.

for patients reacting adversely to other ataraxics

SPARINE was used[3] to treat chronic hospitalized psychotic patients ranging in age from 16 to 88 years. Improvement was noted in 72 percent of 180 patients treated. Psychotherapy was facilitated so that 26 patients were able to be released from the hospital. Of 58 patients who were placed on SPARINE because of complications resulting from other ataraxic therapy, 49 (85 percent) showed resolution of complications and were able to be maintained on SPARINE.

References: 1. Figurelli, F.A.: J. Am. Med. Assoc. *166*:747 (Feb. 15) 1958. 2. Fink, L., and Vlavianos, G.: Psychiat. Quart. *32*:532 (July) 1958. 3. Graffeo, A.J.: Am. J. Psychiat. *116*:842 (March) 1960.

For further information on limitations, administration, and prescribing of SPARINE, see descriptive literature or current Direction Circular.

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Conway, J., and Lauwers, P.: Circulation **21**:21, January, 1960.

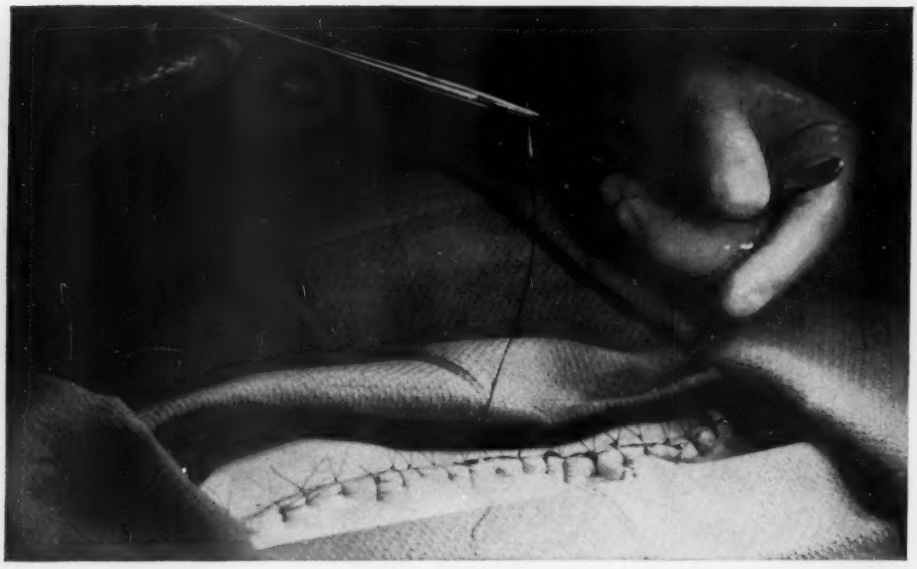
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1. Morani, A. D.: J. Med. Women's Fed. *42*:12, 1960. 2. Cigarroa, L. G.: J. Internat. Coll. Surgeons *34*:442, 1960. 3. Moore, F. T.: Brit. J. Plastic Surg. *11*:335, 1959. 4. Personal Communications to the Medical Department, Armour Pharmaceutical Company, 1959.

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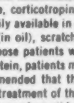


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references: (1) Hirshleifer, I.: Adjunctive therapy in cardiacs, presented at the Spring Scientific Symposium, Connecticut Acad. Gen. Pract., Hartford, Conn., March 16, 1961. (2) Frohman, I. P.: The Alleviation of Stress in the Elderly Cardiac Patient, **ibid.** (3) Kent, E. A.: Management of the Hyperactive Geriatric Patient, **ibid.**

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REFERENCES: 1. DeCourcy, J. L., and DeCourcy, C. B.: *Pheochromocytoma and the General Practitioner*, DeCourcy Clinic, Cincinnati, Ohio, 1952, p. 107. 2. Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: J.A.M.A. *146*:1383 (Aug. 11) 1951.

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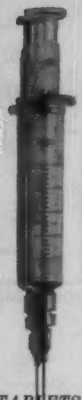
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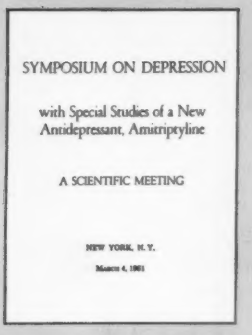
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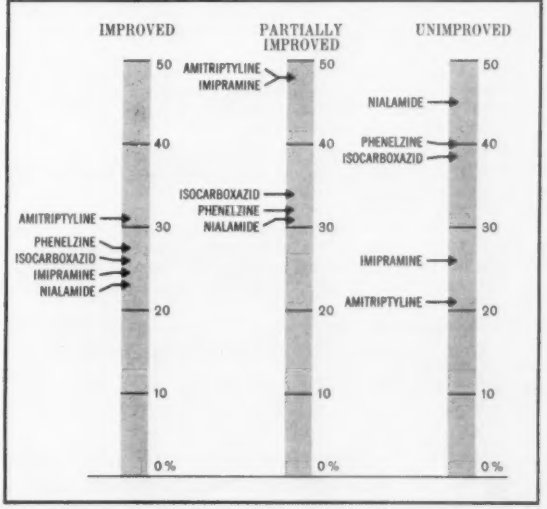
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INVESTIGATOR	FINDINGS
DUNLOP, EDWIN: The treatment of depression in private practice.	"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears . . . to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes. ". . . Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."
BENNETT, DOUGLAS: Treatment of depressive states with amitriptyline.	"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."
SAUNDERS, JOHN C.: Antidepressives: the pith of affective therapy.	"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases. . . . Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."
OSTFELD, ADRIAN M.: Effects of an antidepressant drug on tests of mood and perception.	"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

(This symposium was published in Diseases of the Nervous System, Volume 22, Section Two—Supplement, May 1961)

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. "... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."

COMPARISON OF THERAPEUTIC RESULTS WITH VARIOUS ANTIDEPRESSANTS



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EXCERPTS FROM A SYMPOSIUM ON DEPRESSION (continued)

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INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

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The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. It does, however, augment or may even potentiate the action of MAO inhibitors. Thus, in patients who have been receiving MAO inhibitors, ELAVIL should be instituted cautiously after the effects of the MAO inhibitors have been dissipated. No evidence of drug-induced jaundice, agranulocytosis, or extrapyramidal symptoms has been noted. Side effects with ELAVIL are seldom a problem and are not serious. They are dosage-related and have been readily reversible. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma, prostatic hypertrophy and urinary retention.

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REFERENCES: 1. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 2. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 3. Barsa, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957. 2. Bellet, S.: Amer. Heart J. 56:479, 1958. 3. Bellet, S.: Amer. J. Cardiology 4:268, 1959. 4. Finkelstein, D.: Penn. Med. J. 61:1216, 1958. 5. DiPalma, J. R.: Progress in Cardiovascular Dis. 2:343, 1960.

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Eradication of Poliomyelitis

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POLIOMYELITIS, as well as many other infectious diseases, probably began their association with the human species long before human beings evolved in their present form. A few of these diseases, like smallpox and malaria, have already been eradicated from large parts of the world, although they still continue to contribute to the sum total of misery in other parts inhabited by hundreds of millions of human beings. In the present communication, I should like briefly to review the recently acquired knowledge which justifies the expectation that poliomyelitis may also be eradicated from large areas of the world.

An infectious disease can be eradicated when the chain of transmission necessary for the survival of the infectious agent in nature is broken. In the case of poliomyelitis the work of recent years has established that the alimentary tract of human beings is the primary site for multiplication of the polioviruses, and that these viruses maintain themselves in nature by passing with contaminated feces directly or indirectly from one susceptible human being to another. While polioviruses have been detected in extrahuman sites, such as flies and roaches which have access to human feces, there is no evidence at the present time of a cycle of transmission independent of the human alimentary tract. The work of recent years also established that, following natural infection, the alimentary tract develops a complete or partial resistance to reinfection, which can greatly limit the soil on which the polioviruses have to multiply in order to persist in nature. Under conditions of poor sanitation and hygiene, where almost all children become immune during the first four years of life, the naturally occurring polioviruses maintain themselves without difficulty by continuously involving only a fraction of the total population. On the other hand, in countries with high standards of hygiene and long periods of cold weather, an extensive epidemic year may be followed by many years with only minimal dissemination of the polioviruses,

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until enough newborn children with susceptible intestinal tracts are accumulated to provide a suitable soil for unbroken cycles of transmission. A high incidence of the paralytic disease is associated with a high incidence of viral dissemination when the spreading polioviruses are of high virulence. Recent studies have indicated that naturally occurring polioviruses can be of low, intermediate, or high virulence for the nervous system without reference to their capacity for multiplication in the intestinal tract.

KILLED-VIRUS VACCINE

The development by Salk of the killed-virus vaccine provided a tool with which the incidence of the paralytic disease could be greatly reduced, but many field and experimental studies have now shown that the immunity provided by this vaccine does not prevent multiplication of the polioviruses in the intestinal tract. Thus, in a community in which a large proportion of the population has been protected against paralysis by the Salk vaccine, the polioviruses readily maintain a continuous cycle of transmission and can paralyze those who have never acquired immunity or have lost it. This phenomenon accounts for the continued occurrence of thousands of paralytic cases of poliomyelitis in the United States and of epidemics of considerable magnitude in recent years in Canada, Hungary, and Israel, where the killed-virus vaccine had been administered to the major portion of the susceptible population.

ORAL ATTENUATED VIRUS VACCINE

The immunity produced by orally administered, live attenuated poliovirus vaccine not only protects the individual against paralysis but also alters the susceptibility of the intestinal tract to multiplication of the polioviruses. The extensive work that has now been carried out with the oral poliovirus vaccines permits formulation of the following five basic principles:

1. The selected vaccine strains can multiply extensively in the alimentary tract of human beings, but lack the capacity for significant *in vivo* multiplication in other extraneural tissues and in the central nervous system of higher primates. These properties are the basis for the safety of these strains in human beings, which has now been established for young and old, in millions of persons under the most varied conditions of life and administration of vaccine.

2. The immune response depends on adequate multiplication of each type of poliovirus in the intestinal tract, and manifests itself not only in development of homotypic antibody but also in varying degrees of homotypic resistance of the intestinal tract to reinfection.

3. The degree of subsequent intestinal resistance to reinfection is independent of the antibody in the blood but depends rather on the extent of the initial viral multiplication in the intestinal tract, which is optimal when each type multiplies separately as long as possible without interference from other viruses. This is the basis for administering each of the three types of vaccine separately at intervals of not less than six weeks in parts of the world and at times of the year when interference from other enteric viruses is minimal.

4. A varying proportion of unvaccinated persons becomes immune by intimate contact with young, vaccinated children.

5. Intestinal resistance in a large proportion of the child population leads to a break in the chain of transmission of polioviruses with a consequent protection of the unvaccinated as well as of the vaccinated persons in a community.

The fact that intestinal resistance to reinfection develops after infection by the attenuated polioviruses has now been amply documented by a number of independent investigators in the U. S. A., the USSR, and Holland. The expectation that such intestinal resistance to reinfection in a

large proportion of very young children, who are the most important spreaders of the polioviruses, would lead to a break in the chain of transmission can now be documented both by epidemiologic observations and by extensive virologic studies that were carried out in my laboratory under two totally different field conditions.

EPIDEMIOLOGIC OBSERVATIONS

The first epidemiologic indication that administration of oral poliovirus vaccine to approximately 50% of the susceptible population can suppress the disease in the unvaccinated portion of the population was supplied by M. P. Chumakov and his associates during the field trials of the vaccine in the Spring of 1959 in the republics of Estonia and Lithuania. The usual increase in the summer incidence of the disease was entirely suppressed and the few reported cases were for the most part atypical or isolated facial palsies that were not confirmed as being poliomyelitis. The first steps in the attempt to eradicate poliomyelitis were taken in 1960 in many countries outside the U. S. A., where more than 85 million persons received the oral vaccine, and in the cities of Cincinnati, Ohio, and Rochester, New York, where approximately 300,000 persons received the oral vaccine during relatively brief periods of time in community-wide programs. In Czechoslovakia and Hungary where 90% or more of the pre-school children received all three types of the vaccine prior to the summer of 1960, careful clinical and virologic surveillance of all reported suspect cases indicated that not a single confirmed case of poliomyelitis occurred after July 1 in a total population of close to 25 million persons. The vaccination rate in the USSR was equally high, but precise information is lacking on the extent to which the disease was eliminated after the completion of the vaccination, because of the difficulties involved in checking all the reported cases. In Cincinnati, where only about 73% of the pre-school children received all three types of the vaccine by the end of June, and about 79% of the school children received only the Type 1 vaccine before the summer season, not a single confirmed case of local origin occurred during the entire year. On the other hand in Rochester, N. Y., where Type 1 poliovirus was already spreading early in 1960, the administration of the Type 1 and Type 3 vaccines in May and June respectively to only 20% of the pre-school children and to about 70% of the school children did not prevent the occurrence later in the summer of three paralytic cases of Type 1 poliomyelitis in unvaccinated, noncontact persons. The epidemiologic experiences in the European countries and in Cincinnati show that poliomyelitis can be completely eliminated from a community in a single season by rapid community-wide administration of oral vaccine when about 70% or more of pre-school children are covered by such programs. Of course, one cannot now be certain that a 70% coverage of pre-school children would suffice under all conditions, but it is quite clear from the Rochester experience that any program that reaches only 20% of the pre-school children is inadequate because the naturally occurring polioviruses in the remaining 80% can continue their own cycles of transmission.

VIROLOGIC OBSERVATIONS

Now let me examine the virologic evidence that the feeding of attenuated poliovirus vaccine within a short period of time to a majority of the young children, which inundates a community with poliovirus more extensively and rapidly than any natural epidemic, can actually ultimately break the chain of transmission of polioviruses. Our first study was in Toluca, Mexico, with a population of about 100,000, where more than 90% acquire immunity to poliomyelitis during the first four years of life and pay for it on the average with 14 paralytic cases per year.

A preliminary virologic study on rectal swabs from about 1,600 children and several hundred mothers in August, 1959, indicated that natural infection with all three types of poliovirus and other enteric viruses was extraordinarily high, the incidence of virus isolation from single rectal swabs being as high as 50 to 70%, which means that the actual infection rate was probably close to 100%. The strategy here was to feed a mixture of all three types of poliovirus vaccine as quickly as possible to most of the young children, let nature help in their dissemination and determine (a) whether the polioviruses would temporarily displace the multitude of other enteric viruses, (b) how long the polioviruses would persist in the community, and (c) whether all the children would become immune before the natural transmission of the polioviruses stopped. In August, 1959, the trivalent vaccine was fed within a few days to about 26,000 children, or 86% of the total population from newborn to ten years of age. During the subsequent three months more than 3,000 rectal swabs were tested for virus. We found that after an initial displacement of the other enteric viruses for a period of four to six weeks, the dissemination of polioviruses dropped so markedly that by three months the isolation rate was 16 times lower than before the vaccine was fed. All this happened before all the children were immunized, and it was necessary to give another feeding of vaccine to accomplish within a few months what nature required four years to do—without, of course, paying any price in paralysis. The Toluca experience provides a model for the utilization of oral poliovirus vaccine in that large subtropical and tropical part of the world, where natural immunization during the early years of life is now being achieved at an increasingly higher cost in paralysis.

Our second study began in Cincinnati in April, 1960, where tests on rectal swabs from 1,000 pre-school children, equally divided among lower and higher income families, showed that the incidence of poliomyelitis and other enteric viruses was very low even among the poor families, the total isolation rate being 4.9% in the low income group and 2.2% in the higher income group. Here the three types of oral vaccine were given separately at monthly intervals, beginning at the end of April, in the order of I, III, II, each type being administered to a total of about 67,000 pre-school children within one week. Tests on rectal swabs from about 2,200 vaccinated and unvaccinated children, at different times after administration of the three types of vaccine, showed that an initial extensive spread of polioviruses to unvaccinated, susceptible persons both within the family and outside was followed by a rapid disappearance of polioviruses from the community by the end of September, which is the peak period for dissemination of enteric viruses. Under the conditions obtaining in Cincinnati, 100% of pre-school children who were without antibody developed antibody to all three types after receiving each of the three types of vaccine.

Available data indicate that intestinal resistance may persist for at least two years after vaccination, the longest period tested thus far. It may be expected, therefore, that children born in communities after mass use of oral poliovirus vaccine will have little or no opportunity for natural immunization, and that vaccination for poliomyelitis will have to continue over the years as it is being done for smallpox.

OPTIMAL USE OF THE ORAL VACCINE

A program for the optimal utilization of oral poliovirus vaccine in the U. S. A. and in other comparable countries would, therefore, involve two phases:

1. Community-wide vaccination during the winter and spring months of the year of the largest possible number of persons, regardless of how many doses of Salk vaccine they may have had, with special emphasis on the pre-school children, who are the most important disseminators of the polioviruses. The purpose of this first phase

is not only to immunize those who are not already immune, but also to create enough resistant intestinal tracts to break the chain of transmission of the polioviruses and thereby to protect also those in the family and community who failed to receive the vaccine.

2. Continuing vaccination of all newborn children during their first year of life as part of their regular medical care.

Future serologic, virologic, and epidemiologic surveillance will be required to indicate whether or not it may be necessary to fortify this immunity by refeeding of vaccine, and if so, when.

In oral poliovirus vaccine we now have a simple tool with which we may attempt to rid large parts of the world of both paralytic poliomyelitis and the virulent viruses which cause it. I hope that public health authorities everywhere will now provide the necessary leadership for its use and show us the extent to which poliomyelitis can really be eradicated and stay eradicated.

Summario in Interlingua

Un morbo infectiose pote esser eradicate quando le catena de transmission que es necessari pro le superviventia del agente de infection ha essite disrumpite. In le caso de poliomyelitis, recente investigationes ha demonstrate que le vias alimentari del homines es le sito primari pro le multiplication del virus de poliomyelitis e que iste virus se mantene per passar con le feces, directe- o indirectemente, ab un susceptibile homine al altere. Esseva trovate, in plus, que post un infection natural le vias alimentari disveloppa un resistentia complete o partial contra le re-infection, lo que pote restringer grandemente le terreno in que le virus de poliomyelitis ha le possibilitate de multiplicar se e sin que illo non pote persister in le natura.

Le disveloppamento del vaccino de virus morte per Salk provideva un medio que permitteva reducer grandemente le incidentia del morbo paralytic, sed studios subsequente ha demonstrate que le immunitate assi establite non preveni le multiplication del virus de poliomyelitis in le vias intestinal. Del altere latere, le immunitate que resulta del administration oral de attenuate virus vive de poliomyelitis es capace non solmente a proteger le individuo contra le paralyse sed etiam a alterar le susceptibilitate del vias intestinal pro le multiplication del virus de poliomyelitis. Iste facto es amplemente documentate per le reportos de investigatores mutualmente independente in le Statos Unite, le U.R.S.S., e le Pais Basse.

Un programma pro le utilisation optimal de oral vaccino de virus de poliomyelitis in le Statos Unite e altere comparabile paises consisterea de duo phases. (1) Le prime phase effectuarea le vaccination, a base de communitates complete, del plus grande numero possibile de individuos durante le hiberno e le primavera, sin reguardo al numero de doses de vaccino de Salk que illes ha recipite, con attention special prestate al juvenes de etate pre-scholari qui es le plus importante disseminatores de virus de poliomyelitis. Le objectivo de iste phase esserea non solmente immunisar le subjectos qui es non ancora immun sed etiam crear un sufficiente numero de resistente vias intestinal pro rumper le catena de transmission del virus de poliomyelitis e proteger assi le subjectos in le familia e in le communitate qui non recipe le vaccino. (2) Le secunde phase comprenderea le continue vaccination de omne neonatos durante le prime anno de lor vitas como parte routinari de lor surveliantia medical.

In le vaccino oral de virus de poliomyelitis nos nunc possede un simple instrumento con le qual nos pote interprender le essayo de liberar grande partes del mundo de poliomyelitis paralytic e etiam del virus que causa lo.

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A Long-term Study of Cerebral Vascular Disease

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IN JULY 1956 A LONG-TERM STUDY of cerebral vascular disease was undertaken at Bellevue Hospital. Encouraged by the earlier writings of Fisher and Cameron (1), Millikan, Siekert, and Shick (2, 3), Denny-Brown (4), Kubik and Adams (5), Adams (6), Foley and Wright (7), and Wright and McDevitt (8), and aware of the need to establish the natural history of patients with cerebral vascular disease, the study group developed a protocol with both broad and limited objectives. This paper reports certain characteristics of a group of patients with strokes studied at a large municipal hospital. It presents a detailed analysis of a group of patients selected by a randomizing method for long-term anticoagulant therapy, and their controls. The following questions were considered: What types of cerebral vascular disease are seen in a large municipal hospital with a nonselective admission policy and an active emergency service? How suitable is this patient population for anticoagulant therapy? What benefits may be expected from anticoagulant therapy? What dangers arise when these drugs are used in this type of patient group? Using the patients randomized as controls for a guide, can any statement concerning the natural history of strokes be made?

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From the Second (Cornell) Medical and Neurological Services, Bellevue Hospital, New York N. Y., and the Department of Medicine, Cornell University College of Medicine, New York, N. Y.
This study was supported by The National Institute of Neurological Diseases and Blindness, US Public Health Service Grant No. 3-B-9009.
Requests for reprints should be addressed to Irving S. Wright, M.D., Professor of Clinical Medicine, Cornell University College of Medicine, New York, N. Y.

METHODS OF STUDY

Patients who were admitted to the medical and neurological divisions of the Cornell University Service and the medical division of the Columbia University Service (both at Bellevue Hospital) formed the basis of this study. After the house staff of the respective services had completed its evaluation, the Stroke Study Group was asked to see those patients who the house staff felt had cerebral vascular disease of recent onset. Before being considered for randomization for the anticoagulant phase of the study, every patient had a lumbar puncture and an electrocardiogram. Contraindications for randomization for this particular study were:

1. History unavailable or not clear.
2. Marked depression of consciousness or prolonged coma.
3. Cerebrospinal fluid abnormal or unavailable.
4. Sustained and severe hypertension.
5. Severe hepatic or renal disease.
6. Hemorrhagic diathesis and blood dyscrasia.
7. Active peptic ulcer.

Age alone was not an absolute contraindication to randomization but few patients beyond the age of 80 years were thought suitable for inclusion in this part of the study.

When anticoagulant therapy was insti-

tuted, coumarin derivatives (Dicumarol or warfarin) were used with the aim of maintaining the prothrombin time at two or two and one-half times the control of 14 to 16 seconds, as determined by the Link-Shapiro modification of the one-stage Quick test. Heparin was used infrequently to institute therapy. Randomization was usually possible within 48 hours after entry into the hospital.

It soon became obvious that we were dealing primarily with individuals who had had a completed stroke by the time they entered the hospital and that patients with transient ischemic episodes were not being seen by the study group.

Our methods of study have been described in detail previously (9).

Characteristics of Groups Studied

Table 1 shows the entire series of patients seen through December 31, 1960. Of the 688 patients screened by the study group, 413 were males and 275 were females. Using the criteria outlined above, 204, or slightly less than one-third of the patients, were considered suitable for randomization for the anticoagulant phase of the study. In 190 patients the presence of one or more of the previously described contraindications prevented consideration for randomization. There were 277 individuals who could not be randomized because of administrative problems (e.g., impending transfer to another hospital) or because they were thought to be in the terminal phase of their illness. In addition, there were 67 individuals for whom the use of anticoagulant drugs was considered obligatory. These patients had either rheumatic heart disease with cerebral embolization or concomitant signs of a myocardial infarction. It is of interest that several of the myocardial infarctions were of the silent type, being diagnosed solely by electrocardiographic indications.

Table 1. Composition of Series I

Total Patients		688
Males	413	
Females	275	
Suitable for randomization		204
Treated group	106*	
Control group	98†	
Never randomized		484
Contraindicated	190	
Never drawn	227	
Obligatory	67	

* Includes 14 patients who never received anticoagulants.

† Includes one patient with diagnosis of cerebral abscess at autopsy.

Table 2. Composition of Series II

Total Patients		688
Clinical diagnoses:		
Cerebral embolus		36
Cerebral hemorrhage		79
Primary intracerebral	46	
Primary subarachnoid	33	
Cerebral thrombosis		493
Basilar vertebral tree	87	
Carotid tree	406	
Intracranial lesions simulating stroke		21
Tumor	11	
Subdural hematoma	9	
Cerebral abscess	1	
Indefinite diagnoses		59

The clinical diagnoses considered by the study group are described in Table 2. These clinical diagnoses were matched with autopsy findings in 40% of the patients who died. Cerebral embolus was diagnosed in 36 patients; 79 patients were found to have cerebral hemorrhage; 493 patients were diagnosed as having cerebral thromboses, of which 18% were localized to the basilar vertebral tree. It is important to mention that 21 patients were found to have intracranial lesions which were first diagnosed by the house staff as being due to vascular disease, but which were found after in-

vestigation to be due to other primary lesions. Finally, there were 59 patients whose clinical symptoms and signs probably resulted from vascular disease but for whom a definite diagnosis could not be established. It is possible that in the group diagnosed as having cerebral thrombosis, there were individuals with small cerebral hemmorrhages which did not reach the ventricular system, and that these individuals were misdiagnosed. This may occur in as many as 10 to 20% of such patients (10, 11).

THE RANDOMIZED GROUP

After study by both the house staffs and the study group, 204 patients were found suitable for randomization. By use of selector cards previously arranged in a series of sealed, opaque envelopes, these patients were divided so that 106 of them were used as treated patients, while 98 patients were their controls. Fourteen of the 106 patients never received anticoagulant therapy or did not achieve an effective therapeutic range before they died or were transferred to other hospitals. One of the control group was found to have a cerebral abscess at autopsy and thus had to be dropped from this phase of the study. This patient has been described fully in another report (12).

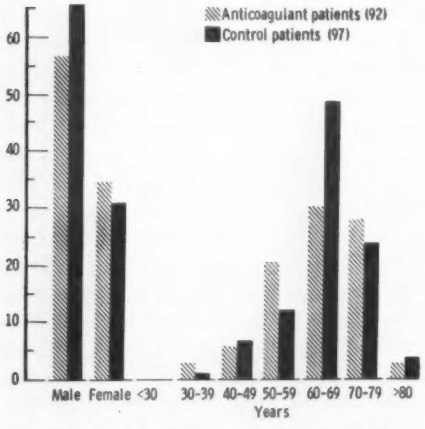


FIGURE 1. Age and sex distribution of randomized group.

TABLE 3. Associated Diseases—Randomized Group

	Treated Group	Control Group
Diabetes	17	22
Hypertension	41	43
Diastolic blood pressure:		
91–100	7	17
101–110	26	19
111–120	8	7
Previous strokes	14	20
Previous ischemic episodes	20	24
Previous myocardial infarction	6	5
Severe peripheral arteriosclerosis	8	3

The randomized group was reduced, therefore, to a total of 92 treated patients and 97 controls.

AGE AND SEX DISTRIBUTION (FIGURE 1)

The age distribution of the two groups is dispersed predominantly through the sixth, seventh, and eighth decades, although the treated group did have a slightly younger population. If one examines the actual ages of the patients as individuals, this difference is found to be quite small. Males predominate in both groups, as they did in the series as a whole. The proportion of elderly patients in this population and the incapacitating nature of cerebral vascular disease has made long-term ambulatory therapy (but not observation) difficult at times in individual patients.

ASSOCIATED DISEASES (TABLE 3)

In addition to the stroke, the group had many other diseases, some of which were felt to affect the severity of cerebral vascular disease. These diseases were distributed fairly evenly between both groups. Seventeen patients in the treated group had clinical diabetes; 22 patients in the control group had this disease. Hypertension was present in 41 patients treated with anticoagulants and in 43 patients serving as controls. Most patients with sustained di-

astolic hypertension were treated with modern antihypertensive drugs. Evidence of prior disease of the cerebral vascular system was present in 34 treated patients and in 44 controls. Many patients failed to seek medical attention during the period of transient ischemic episodes, and even more significantly, their physicians too often had failed to recognize these episodes and their serious implications. Six of the treated patients and five of the controls experienced a myocardial infarction prior to randomization. Severe peripheral arteriosclerosis was present in the lower extremities of eight of the treated patients and of three of the controls. These observations support the concept that a stroke is often but one manifestation of systemic atherosclerosis.

SITE OF THE LESION (TABLE 4)

Seventy-seven of the treated patients developed their lesions in the carotid tree, compared to 73 of the control patients. There were 15 treated patients and 24 control patients with localization of the lesion to the basilar vertebral tree. In retrospect, it would have been better to have had a selector system for each area of cerebral circulation to assure a more even distribution between the two groups. However, we have reason to believe that having survived the initial stroke, the ultimate prognosis may be similar for a lesion in either vascular tree (13).

TABLE 4. Site of Lesion and Composition of Randomized Group

Site of lesion:		
Carotid tree		
Treated group		77
Control group		73
Basilar vertebral tree		
Treated group		15
Control group		24
Treated patients		92
Patient-months observed		1,996
On therapy	892	
Off therapy	1,104	
Control patients		97
Patient-months observed		1,615

TABLE 5. Thromboembolic Complications—Post-randomization

	Treated Group		
	On Anti-coagulants	Off Anti-coagulants	Control Group
New stroke	0	15	17
Recurrent ischemia	0	1	10
Myocardial infarction	1*	1	4
Pulmonary emboli	0	0	5
Thrombophlebitis	0	0	3
Clinical deterioration	3†	0	0
Totals	4	17	39

* Prothrombin time, 19 sec.
† Prothrombin time, 20 sec in one patient.

RESULTS

PERIOD OF OBSERVATION (TABLE 4)

The anticoagulant group has been followed for a total of 1,996 patient-months, of which 892 patient-months were periods during which satisfactory anticoagulant therapy was achieved, and 1,104 patient-months were periods during which the patients did not receive anticoagulant drugs. The control group was followed for a total of 1,615 patient-months. The difficulty connected with the maintenance of prolonged anticoagulant therapy in this patient population has been described by us previously (14). It is inherent in the nature of the patient group dealt with at Bellevue Hospital and need not apply to other groups with different socioeconomic backgrounds.

PERIOD OF POST-RANDOMIZATION

Thromboembolic Complications (Table 5): Thromboembolic complications occurred in 21 (23%) treated patients and in 33 (34%) controls. However, most of the complications in the treated group occurred while the patients were not receiving anticoagulant therapy. In this group, the following complications occurred after anticoagulants had been discontinued: in 15 patients there was a new stroke; one patient experienced several transient ischemic episodes; one patient had an acute myocar-

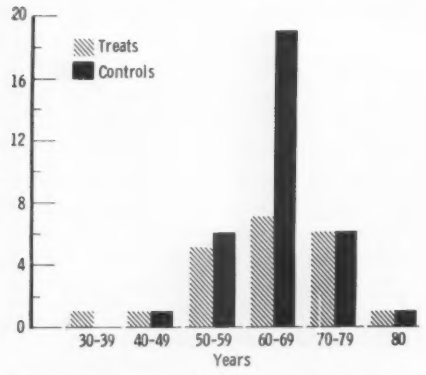


FIGURE 2. Age grouping of post-randomization patients with thromboembolic complications.

dial infarction. During the period of anticoagulant therapy there was one acute myocardial infarction, the prothrombin time of the patient on the first day of the infarction being 19 seconds (i.e., below the desired therapeutic range). In addition, there were three patients whose initial clinical signs deteriorated, only one of whom had a prothrombin time below the desired level. In the control group a total of 39 new thromboembolic events occurred: there were 17 new strokes; ten patients experienced recurrent ischemic episodes; four patients developed an acute myocardial infarction; five patients experienced a pulmonary embolus; severe ileofemoral thrombophlebitis was diagnosed in three individuals.

These figures support the concept that adequately maintained anticoagulant therapy reduces the incidence of recurrent thromboembolic complications in individuals who experience a stroke. However, the benefits to be derived from continuous therapy are not carried over into the period in which therapy has been discontinued.

Age Distribution of Complications (Figure 2): Recurrent thromboembolic complications occurred most frequently in the sixth, seventh, and eighth decades, the age range which included the majority of the randomized group. In the control group they occurred throughout the observation period after randomization, with some greater frequency in the first three months (Figure 3). This is in accord with a previous report of an increased incidence of recurrent thromboembolism during the period of immediate hospitalization (15).

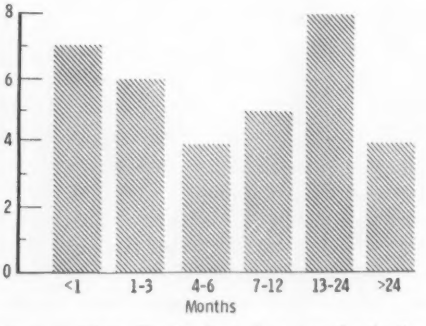


FIGURE 3. Time distribution of post-randomization thromboembolic complications.

TABLE 6. Hemorrhagic Complications—Post-randomization

	Treated Group		
	On Anticoagulants	Off Anticoagulants	Control Group
Central nervous system	3*	1	1
Gastrointestinal system	8	0	0
Genitourinary system	3	0	0
Retroperitoneal space	1	0	0
Tracheostomy site	1	0	0
Hematoma of chest wall	1	0	0
Femoral nerve sheath	1	0	0
Epistaxis	1	0	0
Totals	19	1	1
Deaths	2	1	1

* Two patients were hypertensive.

Hemorrhagic Complications (Table 6): There were 20 hemorrhagic episodes (22%) in the treated group, 19 of which occurred while the patients were receiving anticoagulants. Three of these episodes were fatal, including one which occurred while the patient was off anticoagulant therapy. All of these hemorrhagic events were of such severity that anticoagulant therapy was discontinued. There was but one hemorrhagic episode in the control group, and this was fatal.

The hemorrhages in the treated group

occurred in the fifth, sixth, seventh, and eighth decades, matching the age distribution of the group as a whole (Figure 4). The sites of hemorrhage for both groups are shown in Table 6. In the treated group there were four episodes affecting the central nervous system, one of which occurred at a time when the patient affected was not receiving anticoagulants. Eight hemorrhages occurred in the gastrointestinal tract; three developed within the genitourinary tract; there was one fatal retroperitoneal hemorrhage; one was around a tracheotomy site; one led to a large hematoma of the chest wall; one occurred within

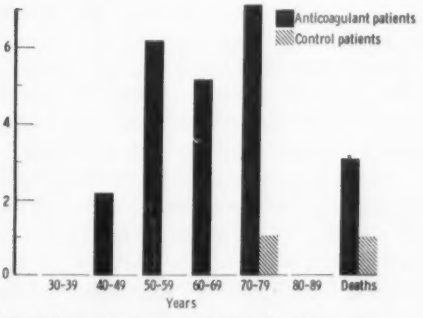


FIGURE 4. Age distribution of hemorrhagic complications post-randomization.

the femoral nerve sheath, leading to femoral nerve compression and dysfunction; and there was one episode of severe epistaxis. The one bleeding episode in the control group was a fatal intracerebral hemorrhage that took place after the patient's discharge from the hospital.

The etiologic factors leading to the development of hemorrhage are shown in Table 7. In seven patients, hemorrhage was related to prolongation of the prothrombin time beyond the accepted therapeutic range, unassociated with a demonstrable pathologic lesion. In six patients the source of bleeding was found, and in one patient it was related to trauma. In five patients no cause was found using the investigative procedures available to us. Two patients with hypertension developed intracranial bleeding, but the hypertension was not of an excessive degree.

TABLE 7. Etiology of Hemorrhage in Treated Patients

Prolonged prothrombin time without demonstrable lesion		7
Underlying lesion		6
Neoplasm	3	
Inflammatory lesion	2	
Surgical site	1	
Trauma		1
Unknown		5

Deaths (Figure 5): At the time of the last follow-up, there were 26 deaths (28%) in the treated group and 35 deaths (36%) in the control group. In the first three months, 16 deaths occurred in the control group, while only seven occurred in the treated group. The causes of death at the time of follow-up are of interest (Table 8). No deaths were due to recurrent thromboembolism while effective therapy was being maintained in the treated group. In the control group there have been a total of 14 deaths due to recurrent thromboembolism (six due to a new stroke, five due to pulmonary embolus, and three due to myocardial infarction). In this series anticoagu-

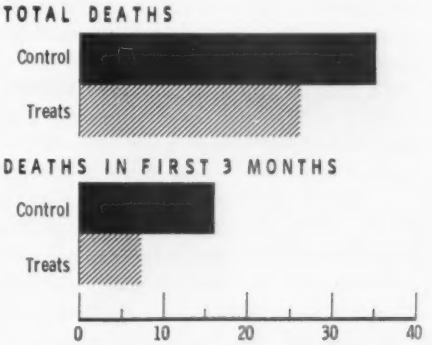


FIGURE 5. Deaths in randomized group, consisting of 92 treated patients observed for 1,996 patient-months, and 97 control patients observed for 1,615 patient-months.

TABLE 8. Causes of Death in Total Series of Randomized Patients

Cause of Death	Patients on Anticoagulants	Control Group
New stroke	5*	6
Pulmonary embolus	0	5
Myocardial infarction	0	3
Initial stroke	3	2
Infection	4	5
Congestive heart failure	6	5
Neoplasm	3	0
Hemorrhage	3†	1
Sudden death, unknown cause	2	5
Trauma	0	3

* Off anticoagulants at time of new stroke.

† One patient off anticoagulants at time of hemorrhage.

lant therapy appears to have been effective in protecting patients with cerebral vascular disease from recurrent thromboembolism.

DISCUSSION

The nature of cerebral vascular disease is such that the prognosis is extremely variable from patient to patient and can be completely unpredictable in a given instance. For this reason a large number of patients, followed for a long period of time and preferably randomized into treated and control groups, must form the basis for any statement concerning the value of a specific therapeutic measure. The present study is based on such a group of patients, who were selected by randomization and who are believed to be as comparable as could be expected without attempting to match cases in pairs. This latter technique would have been a formidable task and would have demanded a far larger number of patients than is presently available to the study group. Comparisons made with respect to age, sex, pre-randomization clinical state, and the nature of the cerebral vascular lesion indicate that the system has been satisfactory.

In addition to establishing comparability, one must clearly state the type of stroke that is being studied. The life history of a cerebral vascular lesion may be divided into three arbitrary stages: (1) recurrent transient ischemic episodes; (2) thrombosis in evolution; (3) the completed stroke.

Millikan, Siekert, and Whisnant (16) and Fisher (17) have demonstrated that anticoagulant therapy can be most effective in abolishing transient ischemic episodes. In addition, Siekert et al. (18) have shown that long-term anticoagulant therapy may prevent the occurrence of late cerebral infarction when given to patients in stage 1. Fisher (17) and Carter (19) have presented evidence indicative of the beneficial effects of anticoagulant therapy in patients with thromboses in evolution. However, one cannot compare patients seen and treated in either stage 1 or stage 2 with patients treated after they have reached stage 3. Our study deals primarily with completed strokes and these have been randomized into the treated and the control groups.

The individuals seen by Millikan were highly selected and screened, and therefore do not give an accurate picture of the nature of cerebral vascular disease seen in a general hospital. The composition of this present study is a more accurate indication of the nature of this disease in an unselected population admitted to a municipal hospital. Unfortunately, the patients served by this hospital do not seek medical aid at a time when they are having ischemic attacks; 23% of the randomized group had experienced ischemic episodes at some time prior to their admission to the hospital.

Patients in stage 1 of cerebral vascular disease are far more suitable for anticoagulant therapy than are those with completed strokes. In our series less than half of the individuals in whom a clinical diagnosis of cerebral thrombosis was made were considered appropriate for randomization. Thus anticoagulant therapy is a more limited therapeutic tool at this stage in the development of a stroke.

Maintenance of long-term anticoagulant therapy can be difficult in individuals with

a completed stroke. We were able to continue therapy of the treated group for less than half of the total observation period. For many patients the necessity of weekly or biweekly visits to the laboratory for prothrombin time determinations precluded continuance of therapy after discharge from the hospital. As yet we do not have the means to bring this therapy to the patient in the nursing home or to the patient confined to his apartment. In addition, some of the patients derived from the socioeconomic group served by Bellevue Hospital disappear and thus are lost to continued therapy upon discharge. These difficulties of long-term anticoagulant therapy do not apply to the same degree in other types of general hospitals or to private patients.

The periods of observation for the randomized group at present are not sufficiently long for the figures concerning the use of anticoagulant drugs to be statistically significant. Nevertheless, these figures strongly suggest the value of anticoagulant therapy, when properly maintained, in reducing the incidence of recurrent thromboembolism and death resulting from it. However, patients on this therapy run the risk of hemorrhagic complications ranging from mild to serious. While this risk can be minimized by respecting the contraindications listed above and by the careful regulation of anticoagulant dosage, it cannot be reduced to zero. There are always some patients with underlying pathology who will bleed more readily when on anticoagulant therapy. Unless one is very careful, there also will be patients who will take large doses of salicylates without the physician's knowledge or who will not report small amounts of bleeding, both of which happened in this study. In addition, there are the difficulties inherent in the nature of the therapy which may lead to bleeding. These have been well discussed in a recent symposium on anticoagulant therapy (20).

The danger of misdiagnosis of a small intracerebral hemorrhage which has not ruptured into the ventricular system or directly into the subarachnoid space is always present when one treats an acute stroke. This risk can be minimized, but not completely eliminated, by careful adherence to the criteria for randomization mentioned previously. More accurate diagnostic methods for detecting patients with this lesion are needed. We have not had any fatalities due to such a mistake, although we may encounter this problem at any time.

Other studies which deal with anticoagulant therapy in patients with completed strokes have been reported (17, 21, 22). The results of these studies are not in accord with our findings. The explanation for the differences may be found in part in the shorter follow-up period of these studies, the inclusion of all degrees of hypertension in the randomized groups and, most important, in differences in the nature of the population groups studied. In addition, there have been reports which are similar to the present one in finding definite value in the use of anticoagulant therapy in completed strokes (23, 24).

While we would agree that anticoagulant therapy cannot be used in a nonselective fashion in patients with completed strokes, it would seem that the case for its use in carefully selected patients is becoming stronger.

Are we in any way affecting the natural history of these patients? A recent report from Worcester, Massachusetts (25), although retrospective in nature, illustrates the tendency for individuals who have recovered from an initial stroke to have recurrent strokes and arterial occlusive disease in other vital areas. The results to date in our control group support these findings. They also re-emphasize the concept that the patient with cerebral vascular disease is very likely to have systemic atherosclerosis. Lacking a specific therapeutic measure for this disease state, it appears

justified to consider the use of anticoagulant therapy as a prophylactic measure in well-selected individuals.

Conclusions

Anticoagulant therapy can be used in no more than one-third of all patients admitted to this large municipal hospital with the diagnosis of cerebral vascular disease.

Long-term anticoagulant therapy, when properly maintained, can be effective in reducing the recurrence of thromboembolic disease in patients with a completed stroke.

Long-term anticoagulant therapy in a population such as that seen at Bellevue Hospital is accompanied by serious hemorrhagic complications in one-fifth of the patients treated. This figure is higher than that obtained from hospitals dealing with patients of a different socioeconomic background or patients seen in private practice.

Long-term anticoagulant therapy would seem to be indicated only in carefully selected patients with a completed stroke.

Summary

In a period of four and one-half years, 688 patients admitted to Bellevue Hospital with an initial diagnosis of cerebral vascular disease were screened by the Stroke Study Group. Four hundred ninety-three of these patients were thought on clinical grounds to have had a cerebral thrombosis. Two hundred four of this group were in turn thought suitable for randomization for the anticoagulant phase of the stroke study. Comparability of 189 of these patients randomized into treated and control groups was established with respect to age and sex distribution, the presence of other disease states affecting morbidity and mortality, site of the lesion, and period of observation.

During the post-randomization period of observation, 33 of 97 control patients experienced 39 recurrent thromboembolic complications. In 21 of the 92 patients in the treated group, 21 thromboembolic complications occurred, but most of these took place after anticoagulant therapy had been discontinued. Hemorrhagic complications occurred in 20 patients receiving anticoagulant drugs. There were two fatalities of a hemorrhagic nature while anticoagulant drugs were being administered. The etiologic factors concerned in the production of hemorrhage are described.

The mortality rate of the treated group was 28%, while that of the control group was 36%. However, while there were 14 deaths in the control group due to recurrent thromboembolism, no deaths occurred in the treated group in the period during which anticoagulant therapy was maintained.

While anticoagulant therapy cannot be used in a routine fashion in patients with cerebral vascular disease, the evidence for its use in carefully selected patients is increasingly strong.

Acknowledgment

The authors wish to acknowledge the assistance of Mr. Herbert Rich, biostatistician, and Miss Kathleen Monahan, Research Assistant, in the preparation of this paper.

Summario in Interlingua

Durante un periodo de quatro annos e medie —ab julio 1956 ad fin de decembre 1960—688 patientes admittite al Hospital Bellevue de New York con le diagnose initial de morbo cerebrovascular esseva scrutinate per le Gruppo de Studio de Apoplexia. Esseva opinate, a base de datos clinic, que 493 de iste patientes habeva habite un thrombose cerebral. Duo centos quatro esseva considerate como appropriate pro le aleatorisation previdite pro le phase anticoagulantic del studio de apoplexias. Pro 189 de iste patientes, aleatorisate in le duo gruppos de (1) patientes tractate e (2) patientes de controlo, comparabilitate esseva establite con respecto al distribution de etate e sexo, le presentia de altere statos pathologic que affice le morbiditate e le mortalitate, le sito del lesion, e le periodo de observation.

Durante le periodo de observation post le aleatorisation, 33 del 97 patientes de controlo experientiava 39 recurrentias de complication thromboembolic. In 21 del 92 patientes tractate con therapia anticoagulante, 21 complicationes

thromboembolic occurreva, sed le majoritate de istos habeva loco post le discontinuation del therapia. Complicationes hemorrhagic occurreva in 20 patientes qui recipeva anticoagulantes. Duo mortes occurreva in consequentia de hemorrhagia in le tractate gruppo durante le periodo quando anticoagulantes esseva administrate; un tal morte occurreva in le gruppo de controlo.

Le mortalitate in le tractate gruppo esseva 28%; illo esseva 36% in le gruppo de controlo. Tamen, durante que 14 mortes occurreva in le gruppo de controlo in consequentia de recurrente thromboembolismos, nulle tal occurreva in le tractate gruppo durante que un efficace therapia anticoagulante esseva mantenite.

Ben que therapia anticoagulante non pote esser usate routinarimente in patientes con morbo cerebro-vascular, le datos arguente in favor de su uso in cautemente seligite patientes deveni progressivemente plus impressionante.

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Mechanisms of Hyponatremia in Chronic Congestive Heart Failure

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RECENT STUDIES HAVE SHOWN that several factors may contribute to the hyponatremia of congestive heart failure. These include electrolyte shifts between intracellular and extracellular compartments (1), abnormal antidiuretic responses (2–6), glomerulotubular imbalance (7–11), lowered osmoreceptor settings (7, 8, 12, 13), and persistence of water intake despite dilution of body fluids. These diverse factors indicate the complexity of this problem and help explain the erratic responses to a strictly empirical approach to therapy.

This study was designed primarily to elucidate the renal mechanisms contributing to the pathogenesis of hyponatremia in congestive heart failure and to devise a diagnostic procedure for classification of these patients based on their osmotic adjustments to water ingestion and restriction. The results have been interpreted in accordance with modern concepts of renal physiology and were found to lend further clinical support to some of the more recent experimental findings.

PROCEDURES AND METHODS

Eighteen edematous patients with congestive heart failure and hyponatremia (plasma sodium concentration 130 mEq per liter or below) were selected from the medical wards of the Jersey City Medical Center. Patients with primary hepatic cirrhosis or obvious intrinsic renal disease were eliminated.

The subjects were maintained on a low sodium diet ranging between 8 and 20 mEq per day for five to seven days prior to and during the study.

They were kept on their usual digitalis maintenance dose but all diuretics were discontinued at least 48 hours before the study began. All patients were maintained on strict bed rest during the course of the study.

The investigation was carried out in the following manner: After 12 hours of fluid restriction, control blood and urine samples were collected at 8 AM of the first day. The patients then ingested a water load of approximately 15 ml per kg of body weight over a 45-minute period. Blood and urine specimens were subsequently collected simultaneously at two to four hour intervals over a 24-hour period. This part of the study was designed to evaluate the patients' osmotic responses to water loading.

The second part of the study was concerned with the osmotic responses to fluid restriction. From 8 PM of the first day and for the following 36 hours, fluids were withheld from the patients' diet, and blood and urine collections were continued as above.

Urine was obtained by spontaneous voiding from patients in Group 1, described below; indwelling catheters were used in the remaining patients.

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Sodium and potassium concentrations of plasma and urine were measured by a Baird flame photometer with an internal lithium standard (14). Osmolalities were determined cryoscopically by a Fiske osmometer. The analysis of endogenous creatinine chromogen was performed by the method of Bonsnes and Taussky (15). All analyses were performed in

TABLE 1

Clinical and Laboratory Findings in 18 Patients with Hyponatremia and Congestive Heart Failure

Subject	Group*	Age	Sex	Heart + disease	Edema	Response to digitalization and diuretics	BUN mg%	CO_2 mM/L	P_{Na} mEq/L	P_K	Disposition	Miscellaneous
GT	I	83	M	AsHD	+	Good	14	26.7	129	3.8	Died 3 mos later	Autopsy: recent myocardial infarction
SO	I	76	F	AsHD	+	Good	18	22.4	125	4.0	Died 1 mo later	Autopsy: cerebral hemorrhage
FT	I	86	M	AsHD	+	Good, diuretics not used	16	24.4	121	3.6	Died 2 wks later	Died in pulmonary edema following saline infusion
AS	I	80	F	AsHD	+	Good	21	20.6	129	3.7	Died 6 mos later	No autopsy
EA	I	73	F	AsHD	+	Good	18	19.9	130	3.6	Alive‡	P_{Na} 129 mEq/L on discharge
JG	I	80	F	AsHD	+	No medication	13	25.6	128	3.9	Alive	P_{Na} 128 mEq/L 2 weeks later
WG	II-A	63	M	AsHD	+++	Poor	26	15.4	127	4.4	Died 3 wks later	Admitted and died with bronchopneumonia. P_{Na} after 1 week moderate water restriction 138 mEq/L
MZ	II-A	68	F	HAsCVD	++++	Poor	28	18.7	126	4.7	Died suddenly 5 weeks later	Diabetes mellitus. P_{Na} 135 mEq/L P_K 7.6 mEq/L on death. BUN 96 mg%. Autopsy: massive renal infarct
AG	II-A	57	F	AsHD	++++	Digitalis intoxication	55	--	124	5.4	Alive	P_{Na} 140 mEq/L, P_K 4.0 mEq/L, BUN 19 mg% on discharge
JA	II-A	66	M	AsHD	++++	Poor	27	18.0	120	4.5	Died 4 wks later	Following mannitol administration, edema ameliorated and P_{Na} 136 mEq/L 1 week later
JZ	II-A	51	M	RHD	++++	Digitalis intoxication	16	21.0	120	4.5	Alive	Studied during digitalis intoxication. P_{Na} 136 mEq/L 1 week later
JE	II-A	60	M	AsHD	++++	Poor	35	19.7	125	4.9	Died 5 days after the study	P_{Na} 131 mEq/L, P_K 5.7 mEq/L, BUN 49 mg%. No autopsy
MM	II-A	47	F	RHD	++++	Poor	26	21.2	117	5.6	Died 4 wks later	Admitted with refractory edema after the study. The patient developed signs and symptoms of subacute bacterial endocarditis with renal involvement. BUN 106 mg%, P_{Na} 124 mEq/L, P_K 6.6 mEq/L on death. No autopsy
MH	II-B	56	F	RHD	++++	Poor	14	25.4	124	4.0	Died 4 days after the study	Autopsy: multiple valvular lesions, cardiac cirrhosis
SG	II-B	61	M	AsHD	++++	Poor	15	24.6	127	3.7	Alive	Admitted with acute pulmonary edema and shock. EKG: acute coronary occlusion. P_{Na} 138 mEq/L 2 weeks later
DT	III	81	M	AsHD	++	Good	14	--	124	4.2	Alive	----
ML	III	82	F	AsHD	+++	Good	23	21.0	121	4.0	Died 4 mos later on readmission	No medication before 1st admission. On second admission, died within 3 hours. Autopsy: recent myocardial infarction
JG	III	79	F	AsHD	+	Good	27	--	128	4.0	Alive	----

* The patients were divided into groups on the basis of their response to a water load (see Results).

† AsHD, arteriosclerotic heart disease; HAsCVD, hypertensive arteriosclerotic cardiovascular disease; RHD, rheumatic heart disease.

‡ Alive signifies that patient was living six months after discharge.

TABLE 2

Data from patient GT, 83 year old male (group I)

Time	Hour	P_{Na} mEq/L	P_K	P_{Cr} mg%	P_{osm} mOsm/kg H_2O	U_{osm}	U/P osmolal ratio	V ml/min	UV_{Na} µEq/min	UV_K	UV_{osm} µOsm/min	C_{cr} ml/min	C_{osm}	C_{H_2O}
8 am*	0	129	3.8	1.26	263	712	(2.71)							
* H_2O 15 ml/kg body weight by mouth, and ad libitum thereafter														
10 am	2	126	3.7	1.28	258	82	0.31	2.92	5.8	17.5	239	54.6	0.92	+2.00
1 pm	5	127	3.8	1.27	259	106	0.41	2.36	7.0	18.9	250	58.1	0.97	+1.39
4 pm	8	128	3.8	1.28	261	273	1.05	0.89	1.8	8.9	243	55.3	0.93	-0.04
7 pm	11	128	3.9	1.28	262	211	0.81	1.14	2.3	11.4	241	55.0	0.92	+0.22
* Nil per os after 8 pm until 8 am														
11 pm	15	129	3.9	1.29	263	465	1.77	0.50	1.0	16.5	233	53.1	0.89	-0.39
2 am	18	129	3.9	1.26	263	642	2.44	0.34	1.0	19.7	218	51.2	0.83	-0.49
6 am	22	129	3.9	1.27	263	706	2.68	0.30	1.2	19.8	212	50.6	0.81	-0.51
8 am*	24	129	4.0	1.27	264	718	2.72	0.28	1.1	9.0	201	50.2	0.76	-0.48
* Dehydration diet														
12 n	28	129	4.0	1.26	263	709	2.69	0.28	1.1	8.7	199	49.8	0.76	-0.48
4 pm	32	128	4.0	1.29	261	692	2.64	0.29	1.2	8.7	201	50.1	0.77	-0.48
8 pm*	36	129	4.0	1.28	263	698	2.66	0.29	1.2	18.3	202	50.4	0.77	-0.48
* Nil per os														
12 mn	40	129	4.1	1.29	263	712	2.71	0.27	1.1	18.6	192	49.6	0.73	-0.46
4 am	44	129	4.1	1.29	263	716	2.72	0.27	1.1	19.2	193	49.5	0.73	-0.46
8 am	48	129	4.1	1.28	264	720	2.73	0.26	1.3	10.9	187	49.0	0.71	-0.45

duplicate. Glomerular filtration rate was approximated by endogenous creatinine clearance. Endogenous creatinine chromogen clearance (C_{cr}) and osmolal and free water clearances (C_{osm}, C_{H_2O}) in milliliters per minute were calculated as follows: $C_{cr} = U_{cr}\,V/P_{cr}$, $C_{osm} = U_{osm}\,V/P_{osm}$, and $C_{H_2O} = V - C_{osm}$, where U_{cr} and P_{cr} represent urine and plasma concentrations of creatinine; V, urine volume in milliliters per minute; and U_{osm} and P_{osm}, the solute concentrations of urine and plasma in milliosmols per kilogram of water. Since blood and urine samples were collected simultaneously, the value for P_{cr} and P_{osm} in the above equations was obtained by averaging two successive plasma values bracketing a single clearance period.

RESULTS

The patients comprised three distinct groups on the basis of their response to a water load. One group responded in a qualitatively normal fashion by the prompt onset of a water diuresis, the second group showed no diuretic response during the 48 hours of the study, while the last group demonstrated a delayed, nocturnal response. In terms of pathophysiology, hyponatremia was related to resetting of the "osmostat" at a subnormal level, glomerulotubular imbalance,* sustained secretion of the antidiuretic hormone, and combinations of these. The results of the dehydra-

* Throughout this report, the term glomerulotubular imbalance is used to signify a substantially reduced glomerular filtration rate in the presence of normal or enhanced reabsorption of sodium and water in the proximal nephron. This study was not designed to distinguish between normal or enhanced tubular reabsorptive capacity. However, whether or not it is increased in an absolute sense, a large decrease in glomerular filtration rate without a proportional fall in reabsorptive capacity can result in a relative exaggeration of tubular function leading to retention of sodium and water.

tion regimen served to confirm and amplify the interpretations based on the response to water loading.

GROUP I—PROMPT RESPONSE TO A WATER LOAD

Six patients showed a prompt diuretic response to the oral administration of tap water. The clinical findings of all patients are summarized in Table 1. Characteristically, the patients of Group 1 had mild edema which was easily controlled by salt restriction, digitalis, or both, and diuretic therapy.

Data from one subject in this group are presented in Table 2. Following an oral water load of 900 ml, there was an early diuresis associated with a fall in plasma osmolality from 263 to 258 mOsm per kg of water. During this time, urinary osmolality reached its lowest point in the study, falling from 712 to 82 mOsm per kg water. Urine volume was relatively high between 8 AM and 1 PM and could account for most of the administered water. Changes in plasma osmolality were reflected by parallel changes in plasma sodium concentration. With dehydration, urine osmolality rose to 720 mOsm per kg of water. Thus, it ranged between 82 and 720 mOsm per kg of water, indicating a reduced but adequate ability to dilute and concentrate the urine.

In Figure 1 are plotted data from three other patients typical of this group. Most characteristic are the urine : plasma osmolal ratios. Although maximal urine : plasma osmolal ratios were somewhat low, they varied in a qualitatively normal fashion in response to water loading and deprivation. In addition it can be observed that despite fluid restriction plasma sodium concentration remained constant at low levels. The ability to inhibit and stimulate antidiuretic hormone secretion at low levels of plasma osmolality is consistent with the syndrome of resetting of the osmoreceptors at a low level (12).

GROUP II—NO RESPONSE TO A WATER LOAD

Nine patients showed no diuresis during the 48-hour period following a water load. In contrast to the previous group these patients were more edematous and tended to be refractory to diuretics. Moreover, water loading was frequently accompanied by mild signs and symptoms of water intoxication.

These patients could be further subdivided into two distinct subgroups. We feel that the first subgroup, designated as Group II-A, manifested severe glomerulotubular imbalance. This group consisted of seven patients who excreted small volumes of urine only slightly hyper-osmolal or

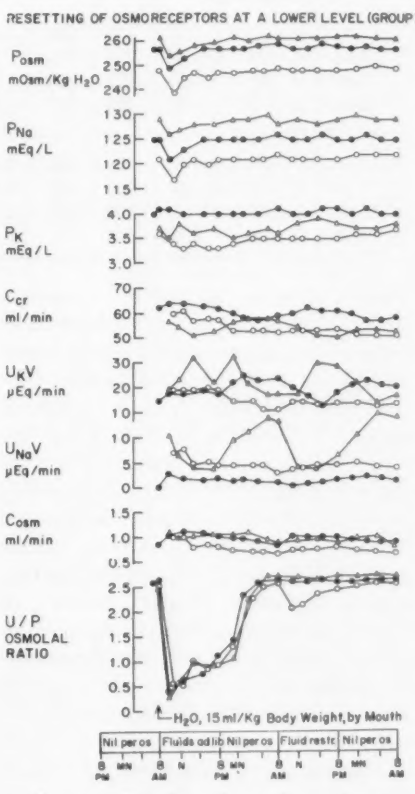


FIGURE 1. Data from three other patients in Group I.

TABLE 3

Data from patient WG, 63 year old male (group II-A)

Time	Hour	P_{Na}	P_K	P_{cr}	P_{osm}	U_{osm}	U/P osmolal ratio	V	UV_{Na}	UV_K	UV_{osm}	C_{cr}	C_{osm}	C_{H_2O}
		mEq/L		mg%	mOsm/kg H_2O			ml/min	μEq/min		μOsm/min	ml/min		
8 am*	0	127	4.4	1.80	260	289	(1.11)							
* H_2O, 15 ml/kg body weight by mouth, and ad libitum thereafter														
10 am	2	122	4.4	1.80	251	217	0.85	0.95	2.9	19.0	206	38.9	0.81	+0.14
1 pm	5	120	4.5	1.83	247	240	0.96	0.82	2.5	13.1	197	38.1	0.79	+0.03
5 pm	9	119	4.5	1.83	245	308	1.25	0.43	0.4	0.9	132	34.0	0.54	-0.11
8 pm*	12	119	4.6	1.83	244	345	1.41	0.33	0.3	0.3	114	32.4	0.47	-0.14
* Nil per os until 8 am														
12 mn	16	120	4.6	1.81	246	309	1.26	0.45	0.5	1.4	139	34.7	0.57	-0.12
4 am	20	122	4.5	1.80	250	229	0.92	0.83	1.7	7.5	190	38.2	0.77	+0.06
8 am*	24	123	4.4	1.78	251	223	0.89	0.91	2.7	15.5	203	39.3	0.81	+0.10
* Dehydration diet														
12 n	28	123	4.5	1.78	252	286	1.14	0.66	1.3	4.0	189	38.0	0.75	-0.09
3 pm	31	124	4.6	1.82	254	314	1.24	0.42	0.4	0.8	132	36.5	0.52	-0.10
6 pm	34	125	4.6	1.83	255	336	1.32	0.36	0.4	0.4	121	32.3	0.48	-0.12
8 pm*	36	125	4.6	1.82	256	317	1.24	0.41	0.4	0.6	130	34.2	0.51	-0.10
* Nil per os														
11 pm	39	126	4.5	1.82	258	306	1.19	0.46	0.5	0.9	141	35.6	0.55	-0.09
2 am	42	127	4.4	1.82	260	267	0.99	0.67	1.3	4.7	179	36.1	0.69	-0.02
5 am	45	128	4.4	1.83	262	235	0.90	0.85	2.5	14.5	200	39.8	0.77	+0.08
8 am	48	130	4.4	1.82	265	221	0.84	0.87	2.6	18.3	192	37.7	0.73	+0.14

hypo-osmolal to plasma, and low in sodium and potassium content. In addition mild azotemia and a tendency toward hyperkalemia were often observed (Table 1).

In Table 3, a study from a patient in Group II-A is presented. Two hours following the ingestion of water, plasma osmolality fell from 260 to 251 mOsm per kg of water. Urine osmolality, however, fell only to 217 mOsm per kg of water during this time. Although plasma osmolality continued to decline progessively, reaching its lowest value of 244 mOsm per kg of water by 8 PM, urine osmolality simultaneously rose to 345 mOsm per kg of water. At 8 PM the dehydration regimen was begun and was continued for the next 36 hours. It can be seen that urine osmolality fell to slightly hypo-osmolal levels during the early morning hours. That afternoon it rose slightly above plasma values but again fell on the following morning. Thus, despite a progressive rise in plasma osmolality during the period of fluid restriction, this patient was excreting hypo-osmolal urine after a 36-hour period of hydropenia and at a time when plasma osmolality had reached its highest value. Over this range of plasma osmolality, then, the sequential changes in urine osmolality appear to be unregulated by plasma osmolality. Indeed they vary in a direction opposite that normally anticipated. This inverse relationship between plasma osmolality and urine osmolality suggests that antidiuretic hormone was absent during the 48 hours of these observations and that the slight degree of urinary concentration and dilution was achieved by glomerulotubular imbalance.

Creatinine clearance and potassium excretion were much lower in this group than in any of the others. Associated with the appearance of hypo-osmolal urine in the early morning hours was a slight increase in sodium and potassium excretion. This probably represents an improvement in glomerulotubular imbalance with more glomerular filtrate reaching the distal nephron. Data from three other representative patients in this group are charted in Figure 2. It is evident that urine : plasma osmolal ratios were never above 1.55. It can also be seen that during the period of fluid restriction plasma sodium concentration and plasma osmolality approached or exceeded pre-hydration values.

The two remaining patients placed in Group II-B were felt to have sustained secretion of antidiuretic hormone. A representative study from a subject in this group is given in Table 4. His data and those of the other patient in this category are plotted in Figure 3. In contrast to the preceding group, these patients excreted a much more concentrated urine containing larger amounts of potassium. Although urine: plasma osmolal ratios were generally above 1.5, rhythmical variations were observed which appeared to be independent of fluid administration or deprivation. As in Group II-A, plasma sodium concentration and plasma osmolality showed a progressive rise to pre-hydration levels during the period of dehydration.

GROUP III—NOCTURNAL RESPONSE TO A WATER LOAD

Three patients showed no response to a water load during the day, but diuresed

TABLE 4

Data from patient MH, 56 year old female (group II-B)

Time	Hour	P_{Na} mEq/L	P_K mEq/L	P_{cr} mg%	P_{osm} mOsm/kg H_2O	U_{osm} mOsm/kg H_2O	U/P osmolal ratio	V ml/min	UV_{Na} μEq/min	UV_K μEq/min	UV_{osm} μOsm/min	C_{cr} ml/min	C_{osm} ml/min	C_{H_2O} ml/min
8 am*	0	124	4.0		254	472	(1.86)							
* H_2O 15 ml/kg body weight by mouth, and ad libitum thereafter														
10 am	2	119	4.0	1.09	244	568	2.28	0.46	0.5	5.5	261	64.0	1.05	-0.59
1 pm	5	118	4.1	1.11	243	621	2.55	0.42	0.4	6.7	261	57.9	1.07	-0.65
4 pm	8	118	4.1	1.09	242	698	2.88	0.36	1.1	17.3	251	59.5	1.04	-0.68
8 pm*	12	118	4.0	1.10	242	679	2.81	0.38	1.5	17.9	258	62.3	1.07	-0.69
* Nil per os until 8 am														
11 pm	15	118	4.0	1.09	244	562	2.31	0.47	1.9	23.0	264	64.2	1.09	-0.62
2 am	18	120	4.1	1.08	243	493	2.02	0.58	2.3	27.8	286	65.6	1.17	-0.59
5 am	21	122	4.1	1.08	250	465	1.89	0.67	3.4	34.2	312	66.8	1.27	-0.60
8 am*	24	123	4.0	1.09	252	401	1.60	0.83	5.8	34.9	333	67.2	1.33	-0.50
* Dehydration diet														
11 am	27	123	4.1	1.12	252	460	1.83	0.61	1.8	31.1	281	65.4	1.12	-0.51
2 pm	30	123	4.0	1.10	251	542	2.16	0.50	1.5	27.0	271	65.1	1.08	-0.58
5 pm	33	123	4.0	1.13	252	665	2.64	0.39	1.6	16.0	259	65.0	1.03	-0.64
8 pm*	36	123	4.1	1.11	253	677	2.68	0.38	1.5	14.9	257	64.8	1.02	-0.64
* Nil per os														
12 mn	40	124	4.0	1.09	254	584	2.30	0.46	1.8	24.4	269	65.2	1.06	-0.60
4 am	44	125	4.0	1.08	256	466	1.83	0.60	2.4	33.6	280	65.9	1.10	-0.50
8 am	48	126	4.1	1.10	258	388	1.51	0.88	6.2	37.0	341	67.3	1.33	-0.45

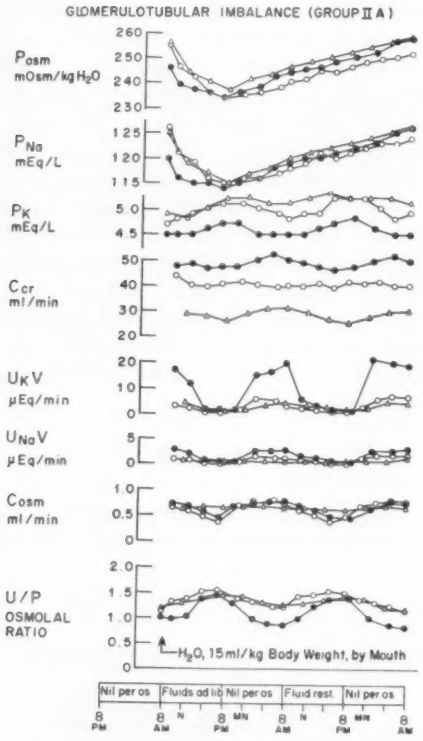


FIGURE 2. Data from three other patients in Group II-A.

briskly at night. Data from one of these patients are summarized in Table 5.

Plasma osmolality and plasma sodium concentration declined as usual following the water load, whereas urine osmolality gradually rose during this same period. Creatinine clearance showed a fall during the day with low rates of sodium and potassium excretion. Between 8 AM and 11 PM the data of this patient were similar to those of patients in Group II-A. However, by 2 AM there was a spontaneous elevation in creatinine clearance which was associated with a pronounced water diuresis and increased rates of sodium and potassium excretion. The kaliuresis was reflected by a concomitant fall in plasma potassium. By 5 AM, plasma osmolality and plasma sodium concentration had returned to prehydration levels.

The restriction of fluid intake begun at 8 PM of the first day was continued during the second day. This was associated with a slight rise in urine osmolality during the day which reached a plateau between 11 AM and 6 PM. However, with the nocturnal increase in creatinine clearance, urine osmolality rose to its highest levels. These changes occurred at low levels of plasma osmolality. It should be noted that the nocturnal increase in creatinine clearance was not dependent upon an increased washout of urinary dead space associated with high rates of urine flow since it also occurred following fluid restriction at low urine flow rates. Figure 4 contains combined data from the three subjects in this group.

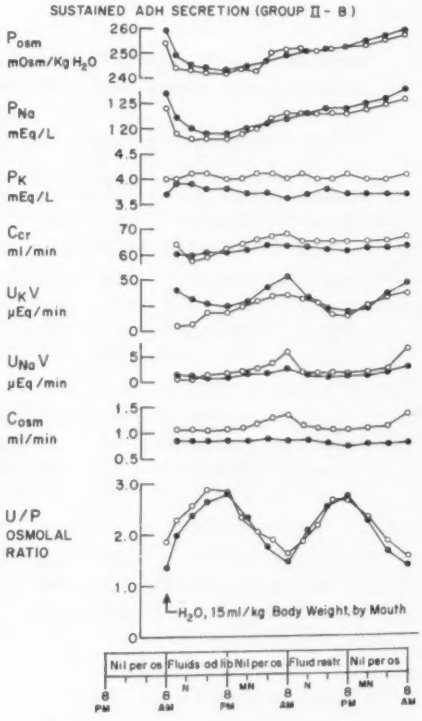


FIGURE 3. Data from the two patients in Group II-B.

TABLE 5

Data from patient DT, 81 year old male (group III)

Time	Hour	P_{Na} mEq/L	P_K	P_{cr} mg%	P_{osm} mOsm/kg H_2O	U_{osm}	U/P osmolal ratio	V ml/min	UV_{Na} µEq/min	UV_K	UV_{osm} µOsm/min	C_{cr} ml/min	C_{osm}	C_{H_2O}
8 am*	0	124	4.2	1.21	253	392	(1.55)							
* H_2O, 15 ml/kg body weight by mouth, and ad libitum thereafter														
10 am	2	120	4.3	1.21	245	300	1.20	0.54	1.1	1.6	162	56.2	0.65	-0.11
1 pm	5	118	4.4	1.22	241	332	1.37	0.44	0.4	0.9	146	50.9	0.60	-0.16
4 pm	8	117	4.5	1.22	240	349	1.45	0.39	0.2	0.4	136	49.7	0.57	-0.18
8 pm*	12	117	4.6	1.23	239	355	1.48	0.33	0	0.3	117	47.6	0.49	0.16
* Nil per os until 8 am														
11 pm	15	118	4.6	1.20	241	258	1.08	0.81	4.1	9.7	209	51.0	0.87	-0.06
2 am	18	122	4.3	1.20	249	76	0.31	4.61	13.8	36.9	350	62.5	1.43	+3.18
5 am	21	124	4.1	1.19	252	101	0.40	3.33	16.7	50.0	366	66.6	1.46	+1.87
8 am*	24	124	4.1	1.19	253	269	1.07	0.97	6.8	13.6	261	60.1	1.03	-0.06
* Dehydration diet														
11 am	27	124	4.2	1.20	253	361	1.43	0.43	1.3	2.6	155	55.7	0.61	-0.18
2 pm	30	123	4.4	1.21	252	462	1.83	0.31	0.3	0.6	143	50.2	0.57	-0.26
6 pm	34	123	4.6	1.22	252	468	1.86	0.25	0.3	0.3	117	47.8	0.46	-0.21
* Nil per os after 8 pm														
10 pm	38	124	4.6	1.20	253	572	2.27	0.35	2.5	4.9	200	50.3	0.79	-0.44
1 am	41	124	4.4	1.18	253	693	2.74	0.48	9.1	23.0	333	60.0	1.32	-0.84
5 am	45	125	4.3	1.19	254	702	2.77	0.52	15.1	48.4	365	64.5	1.44	-0.92
8 am	48	124	4.2	1.20	253	590	2.33	0.41	6.2	13.9	242	59.6	0.95	-0.54

When a water load was administered to one patient shortly before the anticipated increase in creatinine clearance, a prompt diuresis ensued.

COMMENTS

According to present concepts (16–20), the elaboration of a dilute or concentrated urine may be explained by the countercurrent hypothesis first advanced by Wirz, Hargitay, and Kuhn (16), and further studied and developed by Gottschalk and Mylle (17), Ullrich and Jarausch (18), Berliner, Levinsky, Davidson, and Eden (19), and by others. Although many details remain to be established, the following course of events is regarded as a plausible construction of the experimental observations. As the glomerular filtrate flows through the proximal convoluted tubule, solute and water are reabsorbed in equivalent amounts, leaving the tubular fluid isosmotic with plasma at the beginning of Henle's loop (17, 21). In the descending limb of Henle's loop, tubular fluid is concentrated for the first time. This is achieved by the pumping of sodium without water from the ascending limb into the interstitium from which it diffuses into the descending limb. In addition water may diffuse out of the descending limb into the hypertonic interstitium, further contributing to the concentration of descending limb fluid. Thus tubular fluid is concentrated in its downward course along the descending limb and diluted in its upward passage through the ascending limb, forming a countercurrent system. As this effect is multiplied, a graded medullary hypertonicity is produced with maximal intensity at the

papillae. The hairpin-like capillary loops of the medulla assist in the maintenance of medullary hypertonicity by their low blood flow and capacity for countercurrent exchange of diffusible solutes. Regardless of the final concentration of the urine, the fluid entering the first part of the distal convoluted tubule is hypotonic to plasma (17).

In the absence of antidiuretic hormone, the epithelium of the distal convoluted tubule and collecting duct is relatively impermeable to water. Further reabsorption of solute without water in the distal tubule and collecting duct can result in the formation of a markedly dilute urine. When antidiuretic hormone is present, however, the water permeability of this segment increases and, depending upon the quantity of circulating antidiuretic hormone, allows varying degrees of osmotic equilibration to occur between tubular fluid and the hypertonic medullary interstitium. In the presence of normal renal function, urine : plasma osmolal ratios as high as four to one can be achieved (22). In addition to its effects on water permeability, it has been postulated that antidiuretic hormone may increase medullary hypertonicity directly by facilitating sodium transport out of the ascending limb and decreasing medullary blood flow (23).

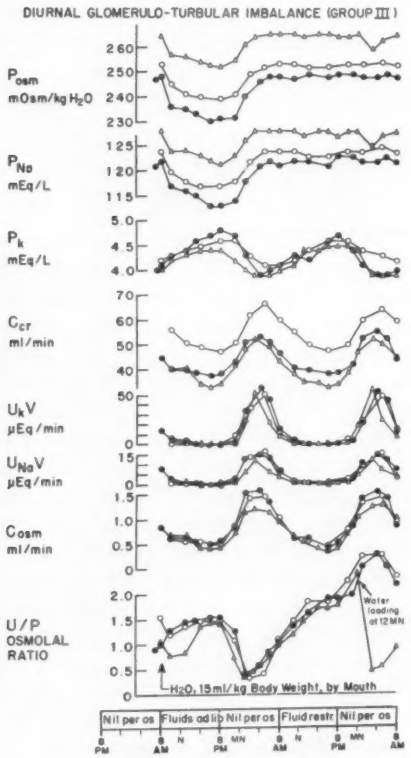


FIGURE 4. Data from the three patients in Group III.

It is thus apparent that the factors necessary for the elaboration of a dilute urine are (1) delivery of a sufficient amount of solute and water to the diluting segment, (2) reabsorption of solute without water in this segment, and (3) the ability to inhibit antidiuretic hormone secretion.

In contrast, urine concentration is dependent upon (1) the production and maintenance of medullary hypertonicity, (2) the secretion of antidiuretic hormone, and (3) the ability of the cells lining the distal tubule and collecting ducts to respond to antidiuretic hormone. However, if glomerular filtration rate is severely reduced in the presence of normal or enhanced proximal reabsorptive capacity, i.e., glomerulotubular imbalance, a markedly reduced quantity of solute and water will reach the distal diluting site. Under such conditions only small amounts of solute-free water can be generated in the diluting segment. The small volume of free water that can be reabsorbed from the distal tubule and collecting duct along an osmotic gradient in the absence of antidiuretic hormone can result in a slightly hyperosmolal urine (24).

GROUP I

The prompt response of these patients to a water load by excreting large amounts of solute-free water indicates that antidiuretic hormone secretion was inhibited

and that the delivery of solute and water to the diluting segment was adequate. Despite their ability to respond to a water load, these patients remained hyponatremic. Dehydration resulted in an increased tubular reabsorption of solute-free water with the elaboration of concentrated urine while plasma osmolality and plasma sodium concentration remained at low levels. The failure of plasma sodium concentration to rise under these conditions of fluid restriction may be explained by the combined ability of the endogenous water of oxidation, preformed water of food, and tubular reabsorption of solute-free water to cover extrarenal water losses.

This qualitatively normal response to water administration and deprivation demonstrates that hyponatremia was not primarily due to renal or neurohypophyseal factors. The ability to inhibit or stimulate antidiuretic hormone secretion at low levels of plasma osmolality indicates a functioning osmoreceptor mechanism which is operating at a lower setting.

Sims et al. (12) described a syndrome of asymptomatic hyponatremia in certain nonedematous patients with chronic pulmonary tuberculosis. They found that the majority of these patients could not correct their hyponatremia in response to sodium loading. The authors concluded that the hyponatremia in these patients was due to resetting of the osmoreceptors and suggested that this situation may be seen in other chronic disorders. Earley and Sanders (13) described a similar condition in six hyponatremic patients with hepatic cirrhosis and edema. They demonstrated the presence of osmoregulation at a low "set" of plasma osmolality by infusing hypotonic and hypertonic solutions.

It has been postulated that this condition may be due to a primary reduction in intracellular osmolality which is secondarily reflected by hypo-osmolality of the extracellular fluid (12, 25). The intracellular potassium deficiency associated with chronic disease states may represent one factor lowering intracellular osmolality (26, 27). Our data supply no information as to how these patients developed resetting of the osmoreceptors, but it might be pointed out that their plasma potassium values were the lowest in the entire series.

GROUP II-A

The outstanding finding in this group of patients was the continued excretion of small volumes of urine only slightly hypoosmolal or hyperosmolal to plasma, despite hydration or dehydration. In addition, creatinine clearance was markedly reduced and mild azotemia was usually present. These findings are consistent with glomerulotubular imbalance.

Berliner and Davidson (24) showed that the diluting ability of the dog kidney may be impaired by reduction of glomerular filtration rate in the absence of antidiuretic hormone. When the glomerular filtration rate of a kidney elaborating markedly hypoosmolal urine was substantially reduced by pneumatic compression of its artery, the urine became progressively less dilute and even concentrated during simultaneous water diuresis in the control kidney. They postulated that the reduction in glomerular filtration rate resulted in an almost complete reabsorption of solute and water in the nephron proximal to the diluting site, interfering with sufficient free water production. Under these conditions the concentrating mechanism was capable of abstracting enough water to produce slightly hypertonic urine in the absence of antidiuretic hormone. It is of interest to note that in their series of experiments, urine hyperosmolality was generally of the order of 300 to 350 mOsm per kg of water. Urine osmolality in our group of patients was strikingly similar, the highest single value being 370 mOsm per kg of water.

In terms of the countercurrent hypothesis, glomerulotubular imbalance can readily explain the formation of slightly hyper-

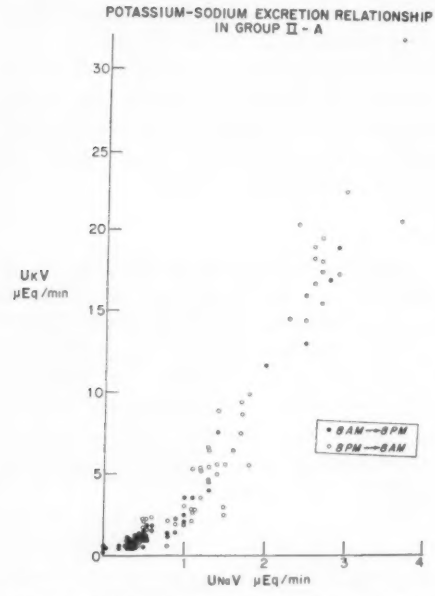


FIGURE 5. Potassium-sodium excretion relationship in Group II-A.

osmolal urine in the absence of antidiuretic hormone. Since the glomerular filtrate in this condition is almost entirely reabsorbed proximally, only small amounts of dilute urine can be produced in the diluting site. The low volume flow of this urine along the collecting duct allows more time for water to diffuse into the hypertonic medullary interstitium, thereby increasing the final concentration of the urine. Because the water permeability of this part of the nephron is low without antidiuretic hormone, complete equilibration would not be expected to occur.

Glomerulotubular imbalance can modify the final urine concentration by another mechanism. Should the delivery of sodium salts and other solutes to the site of countercurrent multiplication be markedly curtailed by proximal reabsorption, maximal medullary hypertonicity could not be achieved. In this situation, final urine osmolality would be proportionately reduced even in the presence of antidiuretic hormone. Levinsky, Davidson, and Berliner (28) have demonstrated this in dogs in which graded reductions of glomerular filtration rate were achieved by pneumatic compression of the renal artery. They found that when it was depressed 30% or more, the urea, sodium, and chloride content of the renal papillae fell markedly. This was reflected by proportionate falls in urine osmolality. Although impaired medullary hypertonicity probably existed in our patients, it cannot be shown from the data since antidiuretic hormone was presumably absent during the period of observation.

Additional evidence for the presence of glomerulotubular imbalance in this group was the persistent excretion of small amounts of sodium and potassium. It is thought at the present time that most of the potassium appearing in the urine is secreted from the distal tubule and collecting duct by ion exchange for sodium (29, 30). The delivery of sodium to the distal exchange site would therefore impose one of the limiting factors for potassium secretion. Consequently, if most of the filtered sodium were reabsorbed proximal to the distal exchange site, potassium excretion would be low. Davidson, Levinsky, and Berliner (31) have clearly demonstrated this relationship in dogs. Moreover, Bell et al. (10) observed an increase in solute-free water and potassium excretion following the infusion of isotonic mannitol solution to patients with congestive heart failure, an effect presumably due to increased delivery of glomerular filtrate to the distal nephron.

The dependence of potassium excretion on sodium in our patients with glomerulotubular imbalance is shown in Figure 5 in which rates of potassium excretion are plotted against those of sodium. It can be seen that a roughly linear relationship is present. The higher excretion rates were generally observed at night indicating some amelioration of glomerulotubular imbalance at this time.

On the basis of this 48-hour study we are unable to exclude an underlying resetting of the osmoreceptors as an additional cause for hyponatremia. However, continuation of moderate fluid restriction in a few of these subjects over several days resulted in a return of plasma sodium concentration to normal.

GROUP II-B

The ability to elaborate a dilute urine in response to a water load is evidence for inhibition of antidiuretic hormone secretion. This effect normally obtains when plasma osmolality is depressed by 1 to 2% (32). Moreover, it has been postulated that a decrease in effective blood volume may be an adequate stimulus for antidiuretic hormone secretion (33). If the secretion is sustained from any cause in the presence of a salt retaining state, expansion and dilution of body fluids will occur.

In these two patients, the most significant observation was the continuous excretion of a highly concentrated urine independent of changes in plasma osmolality induced by water loading or deprivation. The magnitude of the depression in plasma osmolality was greater than that normally required to inhibit antidiuretic hormone secretion. These patients are similar to one patient with congestive heart failure and hyponatremia described by Leaf and Mamby (3). Using a rat bio-assay for antidiuretic hormone activity they concluded that the hyponatremia resulted from sustained secretion of antidiuretic hormone. Their patient also demonstrated the persistent excretion of markedly hypertonic urine and did not respond to a water load.

That urine hyperosmolality in these two subjects was not predominantly due to glomerulotubular imbalance may be deduced from the following considerations: (1) urine: plasma osmolal ratios were considerably higher than those of the preceding group and never fell below unity; (2) creatinine clearance was higher; and (3) potassium excretion was much greater, indicating an adequate delivery of sodium to the distal exchange site.

As shown in Figure 3, there was a rhythmical fluctuation in urine : plasma osmolal ratios. The highest values occurred in the early evening while the lowest were observed in the morning. These smooth variations suggest a daily rhythmicity in antidiuretic hormone secretion which is unrelated to changes in plasma osmolality. The interpretation that variations in the degree of medullary hypertonicity were responsible for this fluctuation is unwarranted since creatinine clearance and total solute excretion did not fall at the lower levels of urine osmolality.

In addition, Weston et al. (5) have shown that the repeated administration of antidiuretic hormone may lead to hyponatremia in patients with congestive heart failure. They gave Pitressin to seven patients with rheumatic heart disease and congestive heart failure and noted the development of hyponatremia with increasing edema.

Antidiuretic hormone secretion is known to occur in response to emotional stimuli of various types (34). These include anxiety, discomfort, and pain. Although the findings in this group were consistent with sustained antidiuretic hormone secretion, its stimulation by repeated venipunctures cannot be excluded. However, since these patients were oliguric and hyponatremic prior to the study, this explanation is unlikely.

GROUP III

Renal hemodynamic studies in healthy adult men reveal that between midnight and 4 AM there is a small but significant decrease in glomerular filtration rate, a greater fall in urine flow, but no significant change in renal plasma flow (35). Other investigations have confirmed these findings and have further demonstrated a nocturnal decline in sodium, potassium, chloride, and bicarbonate excretion (36, 37). On the other

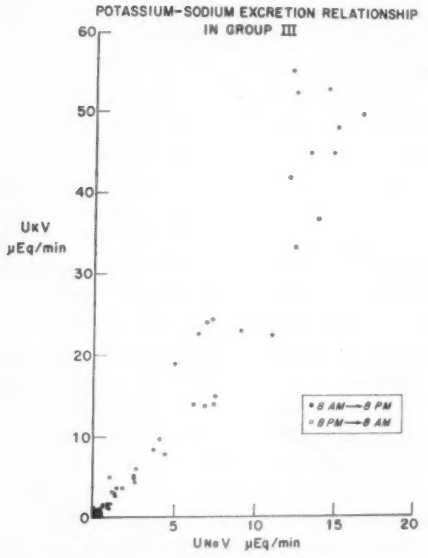


FIGURE 6. Potassium-sodium excretion relationship in Group III.

hand it is well known that a reversal of the normal rhythm may be symptomatic of congestive heart failure and other diseases associated with abnormal water and electrolyte metabolism (38). Brod and Fejfar (39) studied 25 patients with congestive heart failure and found that when nocturia occurred, it was associated with a rise in glomerular filtration rate and renal blood flow.

The three patients in this final group were able to eliminate the morning water load at night. Their diuresis was associated with a significant rise in creatinine clearance and showed the usual features of a water diuresis, that is, a large solute-free water clearance and marked urinary hypoosmolality. The persistent low grade hyperosmolality of their urine during the day with low rates of sodium and potassium excretion was fairly typical of patients with glomerulotubular imbalance. The striking nocturnal diuresis with an increase in creatinine clearance suggests that glomerulotubular imbalance was corrected at this time by increased glomerular filtration. In further support of this interpretation is the simultaneous increase in sodium and potassium excretion which is plotted in Figure 6.

In two of these patients, a sharp increase in urine osmolality and a fall in total solute excretion was observed on the afternoon of the second day, some 16 hours after fluid restriction was begun and prior to any significant increase in creatinine clearance. We interpret this second level of hyperosmolality as marking the onset of endogenous antidiuretic hormone secretion. The maximal urine osmolality observed at this time was 472 mOsm per kg of water. Assuming complete equilibration between collecting duct fluid and the hypertonic medullary interstitium, this finding indicates that medullary hypertonicity is impaired at this level of glomerulotubular imbalance. In association with the spontaneous improvement of creatinine clearance at night, urine osmolality rose to a third new peak as could have been predicted from an increased delivery of sodium salts to the countercurrent site. It would therefore appear that these three degrees of hyperosmolality are caused, respectively, by glomerulotubular imbalance in the absence of antidiuretic hormone, glomerulotubular imbalance in the presence of antidiuretic hormone, and the correction of glomerulotubular imbalance in the presence of antidiuretic hormone. Since these patients dilute and concentrate urine at low levels of plasma osmolality, it is evident that glomerulotubular imbalance was superimposed upon a resetting of their osmoreceptors.

DIFFERENTIAL DIAGNOSIS

In undertaking this investigation, we were primarily interested in devising a reliable screening test for determining the pathophysiology of hyponatremia in chronic congestive heart failure. From the above data it may be seen that there are several differential points separating each

group of patients. For screening purposes, however, we have found that the sequential changes in urine osmolality following water ingestion and deprivation are so characteristic of each group as to be diagnostic by themselves. These patterns are shown in Figure 7. It is apparent that patients with a lowered osmoreceptor setting promptly excreted urine of very low osmolality which increased gradually to the maximum in response to fluid restriction. However, under the same conditions, subjects with glomerulotubular imbalance could not vary urine concentration by more than 100 to 150 mOsm per kg of water. On the other hand, those with diurnal glomerulotubular imbalance characteristically eliminated a dilute urine shortly after midnight and only at this time could they elaborate a maximally concentrated urine following dehydration. Finally, the two patients felt to have sustained antidiuretic hormone secretion elaborated a progressively hyperosmolal urine during the day which declined to lower but still hyperosmolal levels at night.

In subsequent studies we have found that water loading of the magnitude employed in this report is not essential for the elucidation of the underlying pathophysiology. If the patients are simply maintained on fluids ad libitum during the first day and serial urine aliquots analyzed for osmolality, the dangers inherent in water loading may be avoided.

No subject in our series concentrated his urine above 730 mOsm per kg of water. This ceiling on concentrating ability may be related to renal structural changes associated with advanced age, a finding described by other workers (40, 41).

Summary

The pathogenesis of hyponatremia in congestive heart failure was studied in 18 patients by their osmotic responses to water administration and restriction. The mechanisms involved were:

1. Resetting of the osmoreceptors at a lower level.
2. Glomerulotubular imbalance.
3. Sustained antidiuretic hormone secretion.
4. A combination of glomerulotubular imbalance and a low setting of the osmoreceptors.

The possibility of other combinations of these factors could not be excluded. No attempt was made to evaluate the role of potassium deficiency or ionic exchanges between intracellular and extracellular com-

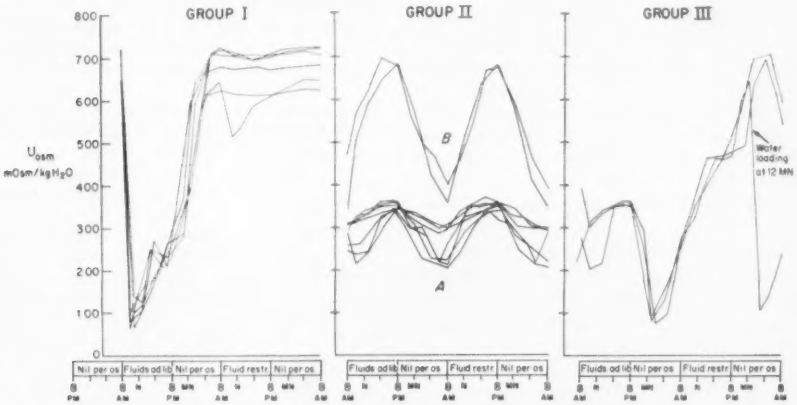


FIGURE 7. Sequential changes in urinary osmolality in 18 patients with hyponatremia and chronic congestive heart failure. Water load begun at 8 AM.

partments, factors which may contribute to hyponatremia.

Summario in Interlingua

Esseva interprendite le essaio de clarificar le mechanismos de hyponatriemia in 18 edematose patientes con congestive disfallimento cardiac, a base de lor responsa al cargation con aqua e al privation de aqua. Specimens de sanguine e urina esseva colligite a intervallos de inter duo e quatro horas. Istos esseva analysate pro creatinina, osmolaritate, natrium, e kalium.

Tres major gruppos de patientes esseva identificate:

1. Sex patientes monstrava un quantitativemente normal diurese post cargation a aqua e elaborava un urina concentrate post privation de liquido. In despecto de iste normal responsas, illes remaneva hyponatriemic. Il esseva supponite que le osmoreceptores de iste patientes esseva re-adjustate a un nivello plus basse.

2. Novem patientes monstrava nulle responsa diuretic a cargation a aqua. Illes esseva dividite in duo sub-gruppos, le un consistente de septe patientes qui habeva un bassissime clearance de creatinina e qui excerneva un micre volumine de urina levemente hyperosmotic o hypo-osmotic que contineva minuscule quantitates de natrium e kalium. Esseva concludite que iste sub-gruppo habeva imbalancia glomerulotubular. Le secunde sub-gruppo que etiam non respondeva al cargation a aqua consisteva de duo patientes qui excerneva un micre quantitate de concentrate urina continente plus grande quantitates de kalium. Esseva concludite que iste patientes habeva un secretion sustenite de hormon antidiuretic.

3. Le tertie gruppo consisteva de tres patientes qui monstrava nulle responsa al cargation a aqua durante le die sed un qualitativemente normal responsa durante le nocte quando lor clearance de creatinina esseva augmentate. In despecto de iste diurese nocturne, iste patientes remaneva hyponatriemic. Esseva concludite que illes habeva diurne imbalancia glomerulotubular, imponite super le re-adjustation del osmoreceptores.

Es presentate un test de differentiation pro determinar le pathophysiologia de hyponatriemia in chronic congestive disfallimento cardiac, a base del responsa urinari a cargation con aqua e a privation de aqua.

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Pathogenesis of Congestive Heart Failure

Effect of Posture and Exercise on Plasma Volume and Plasma Constituents

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THE EXACT MECHANISM of sodium and water retention in congestive heart failure remains obscure despite the fact that hemodynamic, circulatory, renal, and endocrine factors have been studied extensively. Metabolic studies (1–7) have suggested that certain changes occur in the tissue cells which might be responsible for the ultimate accumulation of salt and water. Electrolyte studies of the plasma in heart failure (8, 9) have concurred indirectly with the hypothesis that circulatory insufficiency produces increased cellular osmolality. In view of these changes, further study of the effect of circulatory stress on the extracellular compartment seemed to be indicated.

The effect of posture and exercise on plasma volume has been investigated by other workers (10–18) and although there is general agreement that the volume decreases on standing (14, 15), the exact nature of the fluid lost from the plasma and the mechanism for the transfer of fluid are not known. Furthermore, the effect of exercise itself on plasma volume and plasma constituents has not been clearly established. The present study was conducted to determine the individual effects of posture and exercise on the plasma volume and plasma constituents in compensated cardiac patients. It is hoped that the information obtained on these parameters will help to explain the mechanism of salt and water retention in congestive heart failure.

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METHOD

Trace quantities of radioiodinated serum albumin (10 to 12 μc) were injected into 29 compensated cardiac patients. Serial blood samples were drawn through an indwelling arterial needle during the equilibration period to establish a constant disappearance slope for each individual. Constancy of the disappearance slope during the observation period in these studies was established in four separate cases who remained quietly in the recumbent position for three to four hours. No measurable change in the slope occurred after the first one-half hour period.

In order to study the effect of posture on plasma volume and plasma constituents, eight patients were allowed to equilibrate in the recumbent position for 30 to 60 minutes and then were made to stand idly for 30 to 50 minutes. One patient was made to change his posture successively from recumbency, low Fowler's, sitting, and standing positions. Two patients were stood upright in deep water.

In order to study the effect of exercise 19 patients were subjected to a mild form of exercise consisting of either climbing a two-step platform back and forth or walking slowly on an inclined treadmill after equilibration had been established in the standing position. In

TABLE 1. Effect of Change in Posture (Mean Values)

	No. Pts.	Recumbent	Standing	Change*	*P* Value
Plasma volume, ml/m²	8	1,707 ± 71	1,490 ± 68	−217 ± 11	<.001
Hematocrit, %	8	41.35 ± 1.19	45.66 ± 1.27	+4.3 ± .31	<.001
Plasma osmols, mOs/liter	8	286.8 ± 2.9	287.5 ± 2.6	+0.62 ± 1.25	>.100
Plasma sodium, mEq/liter	6	137.0 ± 1.5	137.3 ± 1.7	+0.33 ± 1.31	>.100
Red cell mass, ml/m²	8	1,034 ± 58	1,066 ± 70	+32 ± 17.7	>.100
Total plasma osmols, mOs/m²	8	490.5 ± 23.8	429.3 ± 22.1	−61.3 ± 4.2	<.001
Total plasma sodium, mEq/m²	6	228.2 ± 9.2	198.6 ± 10.2	−29.7 ± 2.3	<.001
Antecubital venous press., mm Hg	4	7.0 ± 0.5	10.1 ± 1.3	+3.1 ± 1.6	>.100

* ± SE (calculated from analysis of paired values).

seven additional patients both equilibration and exercise were carried out in the recumbent position. The exercise in these patients consisted of either forced adduction and abduction of the legs, or cyclic movement of the legs against mild resistance. At no time was the exercise considered to be exhausting. Visible sweating did not occur in any of the cases.

Duplicate determinations of blood hematocrit, plasma sodium, plasma osmolality and plasma I^{131} radioactivity were made on the samples. Approximately 0.03 milliliter of heparin solution was placed in the syringe to prevent blood clotting. Blood hematocrit was measured in Wintrobe tubes after 30 minutes of centrifugation at 3,000 rev/minute. Plasma sodium was determined by flame photometry. Plasma osmolality was measured with the Fiske osmometer. I^{131} radioactivity was determined in the scintillation well counter.*

Radioactivity of the plasma I^{131} was plotted on semilogarithmic graph paper and the constant disappearance slope for each study was determined. A theoretical I^{131} activity, representing the concentration of an instantaneously mixed isotope within the plasma compartment, was obtained by extrapolation of the disappearance slope to zero time. Plasma volume was then calculated from the total quantity of radioactivity injected divided by the theoretical I^{131} activity at zero time. Subsequent plasma volumes at different intervals were obtained by multiplying the control volume by a ratio of expected plasma activity over observed plasma activity at each interval. Red cell volumes were calculated after the blood hematocrit had been corrected to total body hematocrit by a factor of 0.91 (19).

RESULTS

EFFECT OF POSTURE

Results of the study on the effect of posture are shown in Table 1. The mean disappearance slope of I^{131} activity during rest in the recumbent position was −6.4 ± 3.6% * per hour. Mean plasma volume per unit of body surface area calculated from extrapolation of this slope to zero time was 1,707 ± 219 * ml/m², and the mean red blood cell mass was 1,034 ± 167 * ml/m².

When the positions of the patients were changed from recumbent to standing, the I^{131} count in the plasma rose in each of the eight cases ($P < .001$).† The mean plasma volume decreased and the blood hematocrit rose significantly. Calculated red cell mass changed very little.

The plasma osmolality and sodium concentration did not change appreciably with standing. The total osmolar content of the plasma determined from the observed plasma volume and the osmolar concentration decreased significantly on standing. The mean total sodium content of the plasma likewise decreased on standing.

Changes in plasma volume and plasma constituents with gradual change from re-

* The technical accuracy of the methods used in this study was evaluated by statistical analysis of paired samples. The standard deviation for plasma I^{131} activity was ±1.2%, for plasma osmolality± 2.0 mOsm per liter, for plasma sodium ±2.1 mEq per liter, and for blood hematocrit ±0.27%.

* Standard deviation.

† Calculated from analysis of paired values.

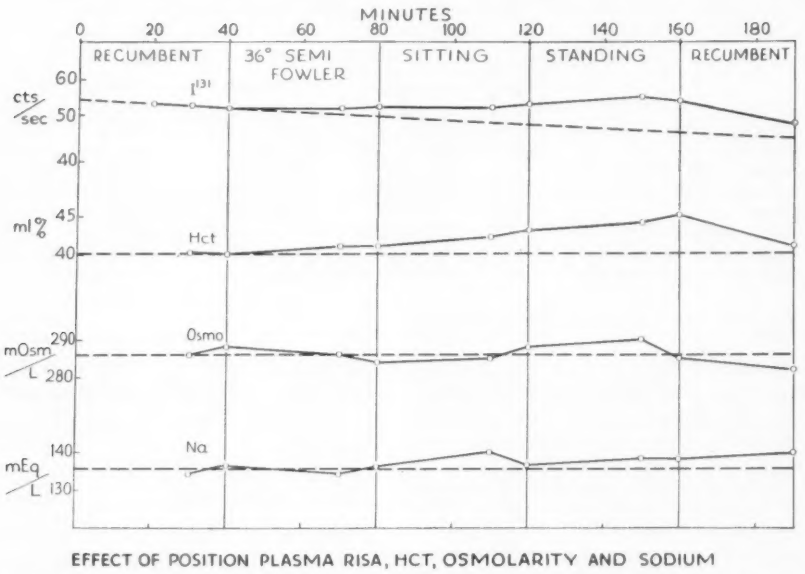


FIGURE 1. *Case 9.* Effect of changes in posture on the disappearance slope of radioiodinated serum albumin, hematocrit value, serum osmolarity, and serum sodium concentration.

cumbency to upright position in one patient are illustrated in Figure 1. A step-like increase in radioactivity reflected a gradual decrease in plasma volume from 3,798 milliliters in recumbency to 3,646 milliliters in low Fowler's, to 3,456 milliliters in sitting, and to 3,266 milliliters in standing positions. The hematocrit and hemoglobin concentration rose proportionately, but plasma sodium and total osmolar concentrations did not vary significantly. With recumbency plasma compartment regained most of the fluid lost on standing, but this was only 50% complete in one-half hour.

When standing was carried out in deep water in two cases, the I^{131} activity did not rise above the expected value but followed precisely the disappearance slope obtained during recumbency. Calculated plasma volumes therefore remained unchanged. Plasma osmolality and plasma sodium did not change but the blood hematocrit and the calculated red cell mass increased. Table 2 presents the data from one of the two patients.

TABLE 2. Effect of Standing in Water (J. O., 46 Yrs., Male, Rheumatic Heart Disease)

	Recumbent out of Water	Standing in Water		Standing out of Water
		10 Min.	25 Min.	25 Min.
Plasma volume, ml/m²	2,112	2,106	2,112	1,998
Hematocrit, %	48.1	49.6	49.3	49.1
Plasma osmols, mOs/liter	283	284	283	283
Plasma sodium, mEq/liter	140	140	144	140
Red cell mass, ml/m²	1,647	1,735	1,716	1,616
Total plasma osmols, mOs/m²	597.7	598.1	597.7	565.4
Total plasma sodium, mEq/m²	295.7	294.8	304.1	279.7

TABLE 3. Effect of Exercise in Standing Position (Mean Values)

	No. Pts.	At Rest Standing	After Exercise 5 Min.	After Exercise 10 Min.	Change at 5 Min.*	P Value	Change at 10 Min.*	P Value
Plasma volume, ml/m²	19	1,507 ± 49	1,440 ± 46	1,472 ± 49	−67 ± 7.6	<.001	−35 ± 5.7	<.001
Hematocrit, %	18	45.8 ± 0.9	46.4 ± 1.0	46.1 ±0.5	+0.6 ± .14	<.001	+0.3 ± .19	>.100
Plasma osmols, mOs/liter	18	287.5 ± 1.6	295.3 ± 2.4	294.0 ± 1.6	+7.8 ± 1.4	<.001	+6.5 ± 1.6	<.001
Plasma sodium, mEq/liter	15	136.8 ± 1.4	142.3 ± 1.6	140.6 ± 1.6	+5.5 ± 0.8	<.001	+3.8 ± 0.8	<.001
Red cell mass, ml/m²	18	1,074 ± 51	1,053 ± 52	1,059 ± 54	−21 ± 5.4	<.010	−15 ± 7.4	<.100
Total plasma osmols, mOs/m²	18	434.9 ± 16.6	427.8 ± 17.2	434.3 ± 16.4	−7.1 ± 3.5	>.050	−0.6 ± 2.9	>.100
Total plasma sodium, mEq/m²	15	201.0 ± 21.4	199.9 ± 22.9	200.8 ± 21.2	−1.2 ± 1.5	>.100	−0.2 ± 1.5	>.100
Antecubital venous press., mm Hg	9	10.5 ± 1.1	12.0 ± 1.6	10.3 ± 1.3	+1.5 ± 1.0	>.100	−0.2 ± 0.9	>.100

* ± SE (calculated from analysis of paired values).

EFFECT OF EXERCISE

Nineteen patients were made to exercise for ten minutes after equilibration of the isotope had been established with the patient in the standing position. In all 19 subjects the isotope count rose significantly with exercise ($P < .001$). Calculation of plasma volumes revealed a significant decrease from a mean of 1,507 ml/m² during idle standing to a mean of 1,440 ml/m² after five minutes of exercise and to 1,472 ml/m² after ten minutes of exercise (Table 3).

Mean blood hematocrit increased significantly after the first five minutes of exercise but changed very little after ten minutes of exercise. The calculated red cell mass actually decreased with exercise ($P < .01$).

In contrast to the effect of posture, exercise produced a sharp rise in plasma osmolality and sodium concentration. In 18 cases studied the mean plasma osmolality rose from 287.5 to 295.3 mOsm per liter after five minutes of exercise and to 294 mOsm per liter after ten minutes of exercise. After seven to ten minutes of rest in the standing position, the mean in 16 patients fell to 289.3 mOsm per liter.

Similarly, mean plasma sodium in 15 patients rose from 136.8 mEq per liter during standing rest to 142.3 mEq per liter after five minutes and to 140.6 mEq per liter after ten minutes of exercise. With rest in the standing position the mean value in 13 of 15 patients returned to near the initial value of 137.2 mEq per liter.*

When the total osmolar content of the

* Exercise in three other patients also produced a sharp rise in plasma radioactive bromide count.

TABLE 4. Effect of Exercise in Recumbent Position (Mean Values)

	No. Pts.	At Rest	After 5 Min. Exercise	Change at 5 Min.*	P Value
Plasma volume, ml/m²	7	2,023 ± 136	1,963 ± 131	−60 ± 6.6	<.001
Hematocrit, %	7	42.6 ± 1.3	43.4 ± 1.3	+0.8 ± 0.2	<.010
Plasma osmols, mOs/liter	3	283	294	+11	
Plasma sodium, mEq/liter	1	139	143	+4	
Red cell mass, ml/m²	7	1,279 ± 83	1,277 ± 88	−2 ± 13	>.100
Total plasma osmols, mOs/m²	3	640	642	+2	
Total plasma sodium, mEq/m²	1	295	295	0	
Rt. atrial press., mm Hg	5	8.1 ± 2.1	11.0 ± 3.0	+2.8 ± 1.4	>.100

* ± SE (calculated from analysis of paired values).

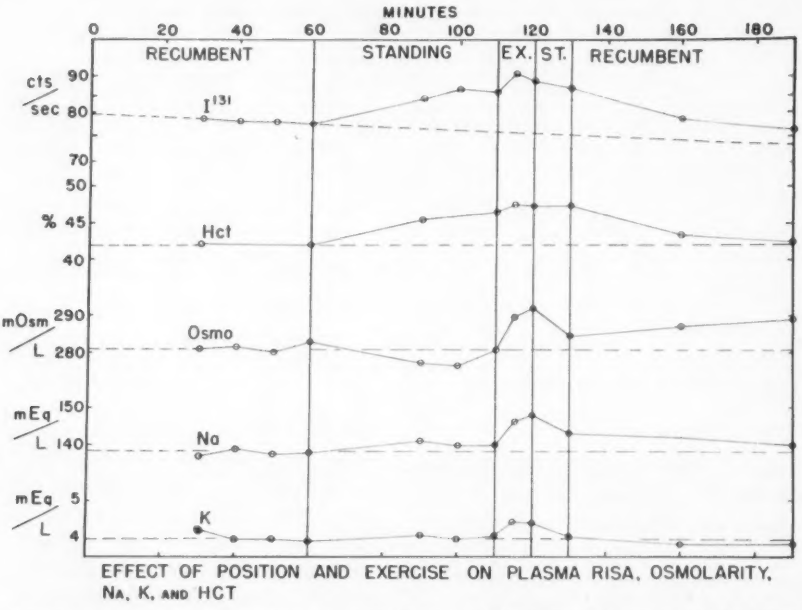


FIGURE 2. *Case 3.* Effect of posture and exercise on the disappearance slope of radioiodinated serum albumin, hematocrit value, serum osmolarity, and serum concentration of sodium and potassium.

entire plasma was calculated, it was found that very little change occurred with exercise: from the mean content of 434.9 at rest to 427.8 at five minutes and 434.3 mOsm per m^2 at ten minutes of exercise. The total sodium content of the entire plasma likewise changed very little with exercise: 201 to 199.9 after five minutes and to 200.8 mEq per m^2 after ten minutes.

The mean increase in peripheral venous pressure measured in nine cases was +1.5 ± 1.0 milliliters mercury ($P > 0.1$).

Seven patients were equilibrated in the recumbent position and then exercised for five minutes in this same position (Table 4). Again, a consistent rise in the plasma I^{131} activity was demonstrated. The calculated mean plasma volume decreased from 2,023 to 1,963 ml/m^2 with exercise. The hematocrit rose slightly but the red cell mass did not change appreciably. Plasma osmolality determined in three cases and plasma sodium concentration in one case all showed a distinct rise with exercise. The total plasma contents, however, were not changed. Right atrial pressures measured in four cases showed a slight insignificant rise.

The effects of both posture and exercise on plasma volume and plasma constituents are illustrated by case D. M. in Figure 2.

DISCUSSION

EFFECT OF POSTURE

The findings confirm the conclusions of others who found a significant decrease of plasma volume on standing. Waterfield (15), using the carbon monoxide method, found a 15% decrease in plasma volume on standing; Thompson, Thompson, and Dailey (14), using a dye method, found a 12% decrease. The present study with radioiodinated serum albumin shows a 12.7 ± 0.24% decrease in plasma volume. The red cell mass changes very little on standing.

It is interesting to note that even a slight change in position from recumbency to a low 36° Fowler's position could be associated with a 173 milliliter decrease in whole blood volume (Figure 1) and that a change to a sitting position could be accompanied by a further 163 milliliter decrease. The beneficial effects seen when cardiac patients in acute pulmonary congestion are allowed to sit up most probably could be explained by the actual fall in circulating blood volume. In the studies of Lagerlöf, Eliasch, Werko, and Bergland (18) there appears to be a reduction in the central blood volume when 60° upright posture is assumed. The magnitude of the central blood volume changes found by Lagerlöf (−230 to −480 milliliters) approximated the total blood volume changes found in our study to suggest that peripheral circulatory volume was maintained whereas central circulatory volume was decreased on standing.

In all probability, loss of plasma fluid from the vascular compartment upon standing was due to increased hydrostatic pressure in the dependent portions, since standing in deep water was not accompanied by a decrease in plasma volume (Table 2). Interestingly, although Leutscher and Curtis (20) had found an increase of aldosterone excretion on standing, Gowenlock, Mills, and Thomas (21) could not demonstrate this when standing was done in deep water. It would appear that at least one of the stimuli which induce aldosterone excretion is a relative decrease in blood volume. The step-like decrease in plasma volume found in one case with gradual change in position also favored the explanation that increased hydrostatic pressure was the cause of the volume changes.

These studies demonstrated gradual reexpansion of the vascular compartment when a recumbent position was resumed by a cardiac patient. The process of transudation back into the vascular compartment was seen to occur within 15 minutes after the subjects were made to lie down, but even after one-half to one hour the maximal effect was not attained. Here again, symptoms of paroxysmal nocturnal dyspnea and orthopnea in cardiac patients could be explained by progressive expansion of the blood volume when recumbent positions are assumed.

The fluid which is forced out of the vascular compartment on standing, for practical purposes, could be called "plasma ultrafiltrate," inasmuch as it has the same osmolar and sodium concentrations as the plasma itself. Calculations disclose a mean osmolar concentration of 272 mOsm per liter and mean sodium concentration of 134 mEq per liter in the fluid emerging from the vascular compartment.

Peripheral antecubital venous pressure in four cases measured from the level of the right atrium did not change consistently with change in position and therefore could not have accounted for the transudation of fluid, although admittedly if the pressure in the veins was raised, the intracapillary pressures would have to increase and allow transudation to occur. Such transudation of fluid apparently could be produced artificially by a series of Valsalva maneuvers which increase the central venous pressure (22).

EFFECT OF EXERCISE

These studies confirmed the findings of Kaltreider and Meneely (12) who demonstrated 230 to 410 milliliters decrease in plasma volume with exercise. In their study the effects of posture were controlled by equilibration of the dye while the subject sat on an upright bicycle. Both the normal and cardiac patients showed a significant decrease in plasma volume. Cardiac patients, as might be expected, were able to do only moderate amounts of exercise compared to the normals who exercised vigorously. In the present study the total

amount and the tempo of exercise were geared only to the estimated degree of tolerance for each patient, and in all cases were submaximal. The greater reduction of plasma volume demonstrated by Kaltreider undoubtedly was due to the fact that greater stress was placed on the circulation and metabolism in their patients than in ours.

The absence of changes in venous or right atrial pressure in a significant number of cases indicates that increased intracapillary pressures were not necessarily responsible for the migration of fluid out of the vascular compartment. Furthermore, since these changes were found to occur in one patient with a permanent tracheostomy, it was felt that a rise in venous pressure which might occur due to an unconscious Valsalva maneuver during exercise was not responsible for the migration of fluid out of the vascular compartments.

None of the patients in these studies visibly perspired during the short period of exercise carried out in the cool morning hours. Furthermore, since calculated plasma compartment showed a tendency to regain its volume after the subjects were made to rest it appeared unlikely that external loss of hypotonic sweat could have accounted for the loss of plasma water during exercise.

Urine excretion in four patients not included in this study decreased during exercise, confirming the results of previous investigators (23). The decrease in plasma volume during exercise therefore could not have occurred as the result of diuresis.

Shrinkage of plasma volume during exercise, without loss of sodium or solutes, indicates transfer of water only out of the vascular compartment. Since increased hydrostatic pressure within the capillaries would force out water and solutes in proportionate quantities (see above) it appears unlikely that loss of plasma water during exercise could be due to any changes of internal pressure within the capillaries. Thus, attraction of water by some extravascular force seems to be a more likely explanation.

Review of the literature on the effect of muscle activity on its composition reveals considerable information which might explain the present findings and which might indirectly shed light on the cause of fluid retention in cardiac patients. As far back as 1865 Ranke (24) found that stimulated fatigued muscle, when exercised and immersed in physiological salt solution, absorbed more water than muscle which had not been stimulated. He also found that as muscles gained water, the blood flowing from exercised muscle lost water and gained solids. He postulated that fatigued muscles imbibe water because of increased quantity of dissociation products in the muscle tissue and that "fatigue increases the osmotic pressure of muscle by breaking down some of the larger molecules into more numerous smaller ones."

Other workers have confirmed Ranke's conclusion. Cooke (25), in 1898, showed that the osmotic pressure in isolated fatigued muscles may be increased by as much as 37.5%. Similar results were obtained by Fletcher (26) in 1904. Muscle exercised with intact circulation was found by other workers to be increased in weight (27), to have lower specific gravity (28), to be increased in volume (29), and to contain more water (30, 31).

Moore (32) in 1916 found the freezing point in fatigued muscle to be more depressed than in resting muscle. When circulation was adequately maintained in the stimulated muscle, depression of the freezing point was not found. Apparently, with intact circulation water entered the muscle cells rapidly enough to mask the increase of osmotically active particles.

Scott, Hermann, and Snell (31) reasoned that if a large mass of muscle was stimulated into activity there would be considerable effect on the blood. They found that by stimulating the leg muscles of a cat or

a dog, an 8.4% increase in red blood cell count and a 3% increase in hemoglobin concentration could be demonstrated. As pointed out above, Ranke had found similar changes in the blood after muscle stimulation. Hyperchloremia observed by Welt, Orloff, Kydd, and Oltman (33) with electroconvulsive therapy was interpreted to indicate an increase of intracellular osmolality.

It was concluded by Ebert and Stead (11) in 1941 that the increase in hematocrit with exercise was not due to mobilization of blood reserves, but actually to decrease in plasma volume since they found a comparable increase in serum proteins and Evans' blue dye concentration. They felt that plasma fluid left the capillaries with exercise. The effect of exercise in their study, however, was probably influenced by change in posture during the period of exercise.

The present study, in which a sensitive method to detect changes in plasma volume was used, showed a consistent loss of plasma water with exercise. It is postulated that water was removed from the circulating blood by the exercised muscle. The stimulus for this transfer most likely resides in the increased cellular osmolality of the activated muscle.

The concept of increased cellular osmolality as a factor in salt and water retention in congestive heart failure was previously developed from studies carried out during recovery from congestive heart failure (1, 4, 7), from biopsied and post-mortem muscle studies (34, 35), and from plasma sodium studies (8, 9) in cardiac patients. Activation of the cellular base in cardiac patients had been confirmed by Squires, Crosley, and Elkinton (2) and considered by Jaenike and Waterhouse (36) as a possible factor in congestive heart failure.

Although no attempt was made in this study to correlate the plasma volume changes with the degree of cardiac competency and the amount of exercise, three of the four patients showing the least percentile volume changes had no history of cardiac decompensation and no gross cardiac enlargement. It is most probable that this phenomenon of migration of water into the cells during exercise is not unique in cardiac patients but is also found in normal individuals exercised vigorously. A rise in plasma sodium concentration had been observed previously in normal subjects undergoing strenuous exercise (8).

Excellent studies performed by Huckabee and Judson (37) offer a possible explanation for the changes found in these studies. Very light exercise carried out by symptomatic cardiac patients produced an increased rate of anaerobic metabolism. Normal subjects were able to perform the same amount of work without any increase of anaerobic metabolism. Thus, the possibility of anaerobic metabolism during exercise producing cellular derangement and increased cellular osmolality becomes worthy of consideration.

It is evident from these studies that the eventual clinical picture of congestive heart failure with pulmonary and peripheral venous congestion and generalized edema could have two distinct components in its pathogenesis; namely, (1) active retention of water and sodium during physical exertion and circulatory stress, and (2) failure to eliminate previously retained water and salt during rest. Shrinkage of plasma volume brought on by exercise, because of the migration of water into the cellular tissue, may initiate reflex retention of water through the volume and osmotic receptors (38–40). Furthermore, during circulatory stress sodium could be retained in order to maintain the osmotic pressure of the plasma equal to that of the elevated osmotic pressure within the cells. Cardiac and circulatory insufficiency could then further contribute to the final picture by causing failure to eliminate completely the previously retained salt and water during rest. The pathogenesis of congestive heart fail-

ure appears to require separate consideration of these two components.

Summary

The effects of change in posture and light exercise on plasma volume and plasma constituents were studied in patients with various forms of mild heart disease. Serial plasma volumes were determined by following the changes in the plasma concentration of injected radioiodinated serum albumin.

When the patients were made to stand from a recumbent position the plasma volume decreased and the hematocrit increased but the plasma osmol and sodium concentrations remained the same. No change in plasma volume occurred when patients were made to stand in deep water. These observations were interpreted to indicate transudation of plasma ultrafiltrate from the capillaries into the interstitial spaces because of increased hydrostatic intracapillary pressure.

When patients were made to exercise lightly on the treadmill or on the two-step platform the plasma volume decreased and the hematocrit, osmol, and sodium concentrations increased. Virtually no change occurred in the total plasma osmol or sodium content. It was felt that circulatory stress of exercise would cause an increase in osmotic pressure of the cells resulting in migration of water from the plasma compartment into the cells. These changes were considered to initiate active renal retention of salt and water in the pathogenesis of congestive heart failure.

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Summario in Interlingua

Studios metabolic e studios del electrolytos in le plasma de patientes in congestive disfallimento cardiac ha indicate que certe alterationes occurre in le cellulas que es possibilemente responsabile pro le ultime accumulation de sal e aqua.

Le effectos del postura e de exercitio super le volumine del plasma e super le constituentes del plasma esseva studiate in patientes levemente cardiac per observar serialmente le alterationes occurrente in le albumina seral marcate per iodo radioactive in le plasma, in le hematocrite, in le pression osmotic, e in le concentrationes de natrium del plasma.

Quando le patientes alterava lor postura ab jacente a stante, le volumine de plasma declinava, le hematocrite montava, e le pression osmotic e le concentration de natrium remaneva le mesmes. Nulle alteration del volumine de plasma occurreva quando le patientes stava in aqua profunde. Iste observationes esseva interpretate como indication del occurrentia de transsudation de ultrafiltrato de plasma ab le capillares ad in le spatios interstitial in consequentia de un augmento del pression hydrostatic intracapillari.

Quando le patientes esseva subjicite a leve formas de exercitio (in le machina a marchar o le platteforma a duo scalas), le volumine del plasma declinava, e le hematocrite, le pression osmotic, e le concentration de natrium cresceva. Le absolute quantitates del constituentes involvite in le pression osmotic e le quantitate absolute de natrium suffreva virtualmente nulle alteration. Esseva opinate que le stress circulatori del exercitio causarea un augmento del pression osmotic del cellulas con le resultato de un migration de aqua ab le plasma ad in le cellulas. Iste alteration initiarea alora un active retention renal de sal e aqua in le pathogenese de congestive disfallimento cardiac.

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The Gastrointestinal Hormones, Secretin and Cholecystokinin-Pancreozymin

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At the end of my lecture for the Gastroenterology Research Group at the World Congress of Gastroenterology in Washington in May 1958 (1) I drew attention to the length of the period between the observation made by a physiologist that a hormone exists and its introduction as a therapeutic or diagnostic tool in medicine. For insulin it lasted 32 years, for heparin, 20 years. Secretin was discovered in 1902, cholecystokinin in 1928, and pancreozymin in 1943, yet they are not commercially available and consequently are not used to the extent that they deserve to be.

The early history of the gastrointestinal hormones has been thoroughly dealt with by Babkin in his monograph of 1950 (2). The further development was touched upon in my previous lecture of 1958, and the history of the chemistry of secretin has been summarized by Mutt in his thesis of 1959 (3). During the last ten years we have been engaged in work trying to make these hormones available for the medical world. Of course it would be desirable to have them in a chemically pure form with all the physical and chemical data registered. But this last stage in the work is nowadays common routine, once one has the pure protein or the peptide. The difficulty with the gastrointestinal hormones is to get them up to this last stage still biologically fully active.

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Secretin

In spite of the interest the medical public showed in secretin from the 1930's and 1940's up to the present time, secretin soon disappeared from the market. Technical difficulties associated with its preparation and the lability of the product can explain its disappearance.

It is therefore not surprising that in the Current List of Medical Literature during the period 1950 to 1957 only an average of five references annually deal with secretin. Cholecystokinin and pancreozymin are not mentioned at all from 1954 to 1957. In the same way as Virchow's cellular pathology one hundred years ago left no place for the study of humoral phenomena, so the dominating interest in vitamins, suprarenal and sex hormones, antibiotics, and other topics completely overshadowed the gastrointestinal field, even if the name "hormone" was created in connection with the discovery of secretin. Thanks to the efforts of the Eli Lilly Co., Indianapolis, secretin has been made available as a public service on special request for research purposes, enabling recent workers to perform their clinical studies in this field.

In fact, during the last years the secretin test has been taken up again in this country and its potentialities definitely demonstrated by Dreiling, Janowitz, and Neiburgs (4, 5) and by Sun, Shay, Chey, and O'Leary (6–8). Interest in it has been greatly stimulated by the possibility of

diagnosing cancer of the pancreas, the bile ducts, and the gall bladder with a combined secretin-cholecystokinin test (5, 9).

A markedly reduced bicarbonate secretion as found on analyzing the duodenal content in the secretin test is considered to be the most reliable test indicating a deficient function of the pancreas gland. It is chiefly chronic pancreatitis, with its decreased water and bicarbonate excretion from the gland, that can be detected by the secretin test, as well as processes impeding the outflow of pancreatic juice, such as duodenitis and carcinoma of the head of the pancreas. It affords a means of differential diagnosis between digestive disorders due to pancreatic secretory deficiency and those due to defective absorption of foodstuffs. In pancreatic atrophy and in cystic fibrosis of the pancreas (10, 11), clearcut answers are obtained by the secretin or the secretin-cholecystokinin test.

THE PROVOCATIVE SERUM ENZYME TEST

In an attempt to eliminate the need for duodenal intubation the changes in serum enzymes in response to secretin or secretin-pancreozymin have been analyzed. Dreiling and Richman in 1954 (12) considered the test to be of little service as a diagnostic tool. However, inflammatory or neoplastic processes in the neighborhood of the papilla of Vater, causing an impediment to the pancreatic flow, are known to cause a regurgitation of enzymes into the blood in the secretin test (13–15).

According to Sun and Shay (6, 7), the serum enzyme response in addition to the conventional study of the duodenal contents increases the value of the secretin test. It will become much more valuable when combined with a pancreozymin/cholecystokinin test. After the collection of a basal 20-minute fraction of the duodenal content, the authors gave 90 units (Crick, Harper, and Raper) of pancreozymin intravenously within five minutes, duodenal contents were collected for a ten-minute period after the beginning of the injection, and then 80 clinical units of secretin were given. In this way a high concentration of enzymes was obtained, evidently advantageous for the test.

In a later communication Shay et al. (8) express still more confidence in the serum enzyme test, as performed by them, starting with pancreozymin (cholecystokinin) followed by secretin. They now consider the provocative serum enzyme test as the most reliable single laboratory response indicating chronic relapsing pancreatitis. They were able to verify the diagnosis in 15 of 31 patients. The authors furthermore found the changes in the serum lipase content to be a somewhat more sensitive indicator than are changes in serum amylase.

HIGHLY PURIFIED SECRETIN

We have elaborated techniques which give us a commercial secretin, 0.03 milligram of which makes up an ordinary dose in the secretin test, a preparation about 1,000 times stronger than the previous ones, which contained 25 to 50 milligrams dry substance or more per dose to be injected. A preparation three times more active, containing about 150,000 Hammarsten cat units (HCU), or 7,500 clinical units per milligram can be obtained. This means that one milligram could stimulate the production of about 13 liters of pancreatic juice, equivalent to 15 liters of 0.1 normal bicarbonate solution.

The decisive step in our work was the elaboration of a new method for preparing from hog intestine a crude concentrate of secretin, pancreozymin, and cholecystokinin on a large scale, to be used as starting material. The purification of this material has been performed by the usual methods of preparative polypeptide chemistry. The bulk of the impurities are removed by fractionating aqueous solutions of the starting material with organic solvents. The partially purified secretin can then

be purified further by electrophoresis on cellulose columns in 0.1 molar ammonium bicarbonate, pH 7.8 to 8.0 (16). All the material migrates to the cathode, the impurities faster than the secretin. The lyophilized active fraction contains 80,000 Hammarsten cat units per milligram.

Alternatively, purification may be achieved by chromatography on carboxymethyl cellulose in 0.02 molar ammonium bicarbonate (17). The lyophilized material from the most active fractions has an activity of about 150,000 Hammarsten cat units per milligram.

At one time we successfully used chromatography on stearic acid. The technique gave us a product with 25,000 Hammarsten cat units per milligram, the purest secretin described in the literature until then. Unfortunately this method was difficult to reproduce.

At present, our purest product has behaved in paper and starch gel electrophoresis and in two-dimensional paper chromatography as if it should be an almost homogeneous protein. Before making final conclusions about its purity, more solvent and buffer systems are to be tried and the behavior of the purest samples in the Craig countercurrent analysis is to be studied. The speed of this analysis will be hampered not only by the easy destructibility of the product, but also by the shortage of material. As soon as we get a lot ready, our clinical friends use it up.

A number of authors have observed an increased flow of lymph through the thoracic duct in the dog and in man after administration of secretin, a flow which was considered to originate in the pancreas. As recently shown by Razin, Feldman, and Dreiling (18) the effect was the same in the dog even after pancreatectomy, but there was almost no effect at all when pure secretin (Vitrum, Stockholm) was used. Evidently the lymph flow was caused by an increased intestinal muscular activity and dilatation of the mesenteric lymphat-

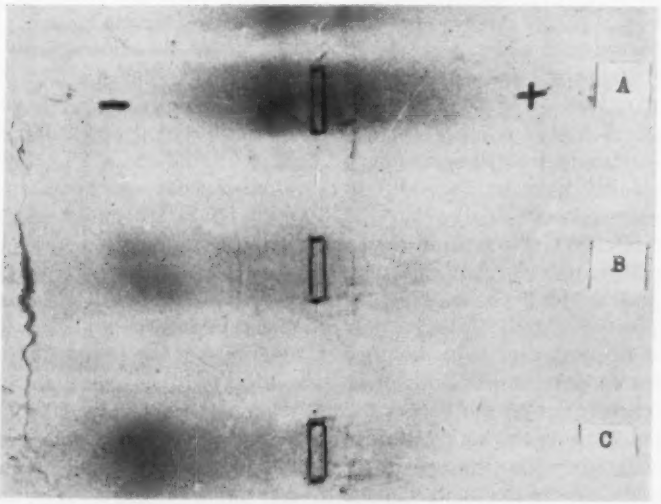


FIGURE 1. High voltage paper electrophoresis of cholecystokinin and secretin (2,000 volts for four hours, with buffer [tris] at pH 9.1 and 6 molar in urea). A. Cholecystokinin, 500 micrograms, after chromatography on triethylaminoethyl cellulose. The cholecystokinin activity migrates towards the anode. B. 250 micrograms of secretin purified on carboxymethyl cellulose. The secretin activity moved towards the cathode, clearly concentrated in the spot. C. 500 micrograms of the same preparation as in B.



FIGURE 2. Starch gel electrophoresis (according to Smithies) showing effect on secretin of chromatography in 0.02 molar ammonium bicarbonate on carboxymethyl cellulose. A and C after chromatography, B before chromatography. (In C the ammonium bicarbonate solution contained 5% N,N'dimethyl formamide. [Electrophoresis buffer: 0.02 M phosphate, pH 6.2, 4 M in urea.] Run for 23 hours at 80 volts, 17 milliamperes, room temperature. Cathodic migration. Nigrosine stain.)

ics elicited by impurities like substance P, villikinin, or *Darmstoff* in the less pure secretin preparations.

The choleretic effect of secretin observed already by Bayliss and Starling has been repeatedly studied both in dogs and in man. Secretin was found to stimulate the liver to the excretion of water, an action analogous with that on the pancreas. This question as well as the question about the secretion of juice from the intestine and the glands of Brunner cannot be discussed without access to pure preparations of secretin. In fact the effect on the liver is still to be observed in using the highly purified secretin. Our group got an increase in the bile flow of 50% in the dog, and Thomas in using one of our preparations with 4,000 clinical units (80,000 cat units) per milligram found in two cholecystectomized dogs with bile fistulae approximately a 100% increase in bile flow over basal secretion. The effect lasted for about 20 minutes. The pure secretin stimulates the excretion from the liver not only of water but also of bicarbonates, as observed recently by Sleisenger and O'Brien (19).

THE STRENGTH OF THE CLINICAL UNIT OF SECRETIN

The relative strength of a secretin preparation can easily be determined by comparing its action in the cat or the dog with that of a standard sample. Within a certain range, complete stoichiometry is present between the quantity of secretin injected intravenously and the quantity of bicarbonate secreted by the pancreas. It is, however, much more difficult to give a figure for the absolute strength, since no international secretin standard exists. We can only rely on evidence from the past regarding the strength of the clinical unit.

Lagerlöf (20) used 16 cat units per kilogram of body weight as the standard dose in the secretin test. Greengard and Ivy counted 20 cat units as one clinical unit. For us, it remains only to judge the strength of the clinical unit by the effect it elicits in man. Lagerlöf found, in 48 healthy subjects, the mean volume of pancreatic juice collected in 60 minutes to be 202 ± 4 milliliters (2.2 to 5.5 milliliters per kilogram body weight), the corresponding figure for bicarbonate being 194 ± 6 milliliters 0.1 normal.

In 1950 Dreiling (21) made a statistical study in 172 normal persons of the response in the secretin test as to volume and alkalinity of the pancreatic juice after one clinical unit of secretin per kilogram body weight. The secretin used was delivered by Astra in Sweden and by the Wyeth Co., Philadelphia, an equal number of persons being treated with each of the two brands. The collecting period was 80 minutes. The frequency distribution curve of the data for people with no pancreatic disorder was essentially symmetrical with a range between 2.0 and 4.4 milliliters of pancreatic

juice per kilogram body weight, mean 3.57 ± 0.68 milliliters.

In administering one clinical unit per kilogram body weight of the Eli Lilly secretin to 123 normal subjects, and collecting the duodenal content during four 20-minute periods, Dreiling and Janowitz (4) found on an average 3.22 milliliters per kilogram (lower limit 2.0 milliliters) and maximal sodium bicarbonate concentration 107 milliequivalents per liter (lower limit 90).

The technique of Dreiling is generally accepted (22), even if some authors prefer to use the 60-minute values. This consequently should be the lead to follow in adjusting the strength of the clinical unit of secretin, of which for practical reasons one unit is to be given per kilogram body weight (in infants twice the amount).

We have used a standard sample of secretin of our own, assayed in 209 tests at 8,400 cat units per milligram, one unit equaling 0.1 milliliter 0.1 normal sodium bicarbonate. One microgram of the standard produced 1.11 ± 0.17 milliliters of pancreatic juice in the anesthetized cat (46 tests), 1.5 micrograms produced 1.38 ± 0.32 milliliters (20 tests), 2 micrograms produced 1.68 ± 0.163 milliliters (118 tests) and 3 micrograms produced 2.40 ± 0.51 milliliters (25 tests). Twenty cat units are taken as a clinical unit.

Mutt and Söderberg (23) have improved the technique of assaying the potency of the secretin and pancreozymin preparations. The major change from the previous technique is that the anesthetized cat with a cannula in the pancreatic duct is kept alive for several days, sometimes for a week. A long-acting anesthetic, ethchlorvynol (Placidyl, Abbott) is administered into the jejunum through an inlaying plastic tube. The gastric juice is continuously evacuated through a gastric fistula, the bladder is emptied, and penicillin and a small dose of heparin are given at regular intervals. The body temperature is kept as close as possible to 37 C by means of a lamp or by heating the table from beneath. This technique saves much labor and allows many more analyses to be performed in a week, a very essential thing for the progress of the work. The cats are on hand early in the morning and late at night just like any other titration machines.

Because of the uncertainty as to the stability of the highly purified secretin and the variability of the individual response in man, it will be difficult to make any statements about the appropriate size of the clinical unit. The only fairly accurate figure obtainable at present is that expressing the strength in cat or dog units at the time of manufacture. Further experience will show at what level the clinical unit is to be fixed, whether 20 cat units will suffice or not.

Cholecystokinin

During the 30 years which elapsed since the discovery of cholecystokinin by Ivy and Oldberg, and its recognition as a specific hormone with a function of causing contractions of the gall bladder it found no practical application in medicine. The product described by Ivy, Oldberg, Drewyer, and Orndoff in the years between 1928 and 1955 (24–27) was used in experiments on a few persons only, and the samples of pancreozymin used by Duncan, Harper, Howat, Oleesky, Varley, and Scott (28–30) in England for producing contractions of the gall bladder were impure, 150 to 200 milligrams of substance being the necessary dose in man. Side effects made these preparations unsuitable for clinical use.

In 1955 we succeeded in preparing a cholecystokinin, with 22 to 25 Ivy dog units per milligram, 2 to 4 milligrams of which, when given intravenously in man, caused a vigorous contraction of the gall bladder. The samples also exerted an action on the pancreas, which Harper, who in 1959 kindly analyzed our samples, found to be 100 times stronger than that of his

original pancreozymin preparations. A variety of studies have now been made with our cholecystokinin preparations.

Edholm (31) studied the action on the normal gall bladder in 15 healthy medical students aged 21 to 26 years. They were given 75 Ivy dog units of cholecystokinin intravenously or approximately one unit per kilogram body weight. The initial volume of the gall bladder varied between 60 and 14 milliliters with an average of 33 milliliters.

After the injection of the cholecystokinin, all gall bladders evacuated a varying amount of their contents. The greatest volume expelled was 27 milliliters and the smallest was 8 milliliters. The average evacuation was 15 milliliters (45%). The main emptying was finished after 15 minutes. Then there was a standstill for another 15 minutes, and 30 minutes after injection refilling began. None of the students felt any pain during the emptying.

Sandblom, Voegtlin, and Ivy showed in 1935 (32) that cholecystokinin dilates the sphincter of Oddi. As demonstrated by Torsoli, Ramorino, Colagrande, and Demaio in Rome (33), the terminal part of the common bile duct is constricted during the first 30 seconds after injection of cholecystokinin. Then follows a relaxation of the musculature and a dilatation of both the intramural and extramural parts of the common duct. Even when the intramural part is organically obstructed, the relaxation is still evident in the extramural part. Cholecystokinin may at least temporarily reduce pure Oddi hypertonicity. It is considered by Torsoli to be the most powerful relaxing agent of the sphincter of Oddi we have today, a detail which evidently offers new diagnostic and therapeutic possibilities for the future. Injection of one Ivy dog unit of cholecystokinin per kilogram body weight will become a specific functional test for the choledochoduodenal junction, and before trying to remove concrements by rinsing the common duct during operation, administration of cholecystokinin is advisable.

The hormone also influences the duodenal motility as demonstrated by Adlercreutz, Pettersson, Adlercreutz, Gribbe, and Wegelius (34) in Helsingfors, and by Torsoli et al. (33). After the intravenous injection of cholecystokinin a tonic relaxation of the second part of the duodenum occurs. The duodenal loop is distended and movements are depressed for a few minutes until the bile enters the duodenum, exerting its strong stimulant action on the intestine. In a cholecystectomized patient Adlercreutz found the inhibition of peristalsis of the duodenum caused by cholecystokinin to last for ten to 15 minutes.

CLINICAL USE OF CHOLECYSTOKININ

Clinical tests in using cholecystokinin as an adjuvant in cholecystography were begun in Stockholm in 1955. The contractility of the gall bladder previously filled with an opaque medium, and the patency of the bile ducts could be studied. This could now be achieved more efficiently and in a shorter time than by using the fat meal of Boyden. More than 30,000 such tests have now been performed in Sweden and elsewhere.

The cholecystokinin test is more reliable than the cream egg yolk meal (35). It also works more quickly, a very essential point in X-ray departments.

Furthermore, since no food has been taken, an X-ray analysis of the stomach can be performed at the same time.

Nordentoft (36), of Aalborg's Amtssygehus, Denmark, found, in making peroral cholecystography with iopanoic acid (Telepaque), that the use of cholecystokinin in connection with massage of the epigastric region gives contraction of the gall bladder with visualization of the bile ducts within 3 to 5 minutes in about 80% of the cases. This technique makes the intravenous cholangiography with Biligrafin superfluous

in about 60% of the cases, where it would be necessary for duct visualization.

A quite extensive evaluation of cholecystokinin in the roentgenological analysis has been made by Bakke (37) in Bergen, Norway, during recent years. In his studies of the function of the gall bladder in healthy and diseased states, he came to two important conclusions. In the Boyden test 30 drops of 2 normal hydrochloric acid should be added to the 150 milliliters of cream and the beaten egg yolk, and, secondly, the gall bladder should, like the stomach, be emptied before starting a roentgenological analysis. The hydrochloric acid greatly enhances the effect of the fat meal.

The roentgenologically transparent bile, filling possibly more than half the gall bladder at the beginning of an analysis, causes a delay in the visualization of the gall bladder and of the ducts after the injection of Biligrafin. Furthermore, the structure of the mucous membrane of the gall bladder can be more clearly pictured when the contrast material enters an empty cavity. Emptying was achieved by giving a fat meal in the evening or by injecting cholecystokinin in the morning half an hour before injecting Biligrafin.

The regular use of cholecystokinin and the performance of the X-ray analysis after filling an empty gall bladder with the opaque medium facilitates the diagnosis of diverticulosis vesicae felleae, diverticula of the sinuses of Rokitansky-Aschoff. Thus, Edholm of Karolinska Sjukhuset recently found two such cases, whereas only one had been observed at the same department during the last 14 years.

Consequently, there are definite indications for the use of cholecystokinin in the routine work of the roentgenological departments.

The Combined Cholecystokinin Secretin Test

There are, however, other indications for utilizing cholecystokinin. The value of the ordinary secretin test is greatly enhanced if it can be combined with a cholecystokinin test, the latter being given one hour after the secretin or in the reverse order as suggested by Dreiling et al. (5) and by Sun et al. (7, 8). The use of cholecystokinin and secretin in succession offers the possibility of analyzing the bile and the pancreatic juice separately. Since cholecystokinin preparations exert a strong pancreozymin action, the capacity of the pancreas gland to excrete enzymes will then be more efficiently demonstrated. If pancreozymin-cholecystokinin is given first the provocative serum enzyme test comes out more distinctly. Since the juices are not contaminated with digestion products, they can be analyzed for both normal components and for the presence of leukocytes, bacteria, and cancer cells. Cholecystokinin furthermore offers the possibility of washing out the bile ducts at will and of getting bile not contaminated with digestion products. Thus, Duncan et al. (28) found the combined secretin-cholecystokinin test to be of particular value in diagnosing deficient gall bladder function. They found the amount of bilirubin delivered to the duodenum after cholecystokinin injection to be highly reduced in chronic cholecystitis. The Meulengracht values found in the duodenal contents collected during the first ten minutes were between 102 and 300 (mean 170) in nine normal persons. In chronic cholecystitis they never exceeded 40. Without a stimulant, values of 0 to 12 (mean 3) were obtained.

Recently the problem of the cytological diagnosis of cancer of the pancreas, the duodenum, and the bile ducts has been studied. Malignant cells can be demonstrated in the duodenal juice after secretin stimulation of the pancreas. Bowden and Papanicolaou (9) presented their material in 1960. They found that ten of 24 patients known to have or subsequently shown to have cancer of the body or the tail of the pancreas, showed a strongly suggestive or

definitely malignant cell picture, and ten showed suspicious findings. Dreiling et al. (5) presented still more convincing material, of which only some details may be mentioned here. Thus, in 24 of 27 patients with cancer of the body or the tail of the pancreas a positive cytological diagnosis was obtained in the secretin test. Malignancy in these parts of the pancreas is otherwise most difficult to detect without surgery. Twenty-one of 23 patients with chronic pancreatitis showed, as expected, an abnormal secretin test and a clearly negative cytology.

It is evident that the combined cholecystokinin-secretin test, in which the contents of the gall bladder and the bile ducts are made available, should be still more valuable in this respect than the secretin test alone. In 12 cases with malignancy, two of the liver, two of the gall bladder, three of the common duct, three of the stomach, and two of the jejunum, Dreiling and his co-workers found a positive cytology for cancer with a normal pancreatic function in all of them.

The Ivy Dog Unit of Cholecystokinin

In comparing the different techniques applied in assaying the biological activity of cholecystokinin, preference is to be given to that used in the laboratory of Dr. A. C. Ivy, the discoverer of cholecystokinin, whose experience now extends over a period of 30 years. The technique elaborated by Denton, Gershbein, and Ivy (38) is easily reproducible and works with great accuracy. A full account of the details of the method used in assaying both secretin and cholecystokinin on cats and on dogs was recently given by Ivy and Janecek (39).

The same preference must also be given to the dog unit of cholecystokinin suggested by Ivy. It has a very suitable strength, because, as we have found, an optimal contraction of the gall bladder is usually obtained in man, when one Ivy dog unit of cholecystokinin per kilogram body weight is administered intravenously.

Purification of Cholecystokinin-Pancreozymin

Our secretin-cholecystokinin-pancreozymin concentrate was treated as described by Mutt (3) in 1959 for the purification of secretin until the extraction of secretin into methanol.

The material insoluble in methanol was washed with ether and dried in air. The yield was 5 g from 1,000 hogs.

The material was then dissolved in water to a concentration of 5 g per 100 ml solution. The pH was adjusted to 7.5 to 8.0 and the impurities that precipitated were filtered off after the addition of 2 g of Hyflo Super-cel per 100 ml suspension. The pH of the filtrate was adjusted to 6.5 with hydrochloric acid and the solution was passed through a column of carboxymethyl cellulose equilibrated with sodium phosphate buffer, pH 6.5, 0.02 molar in sodium. The column was washed with the buffer until practically no protein could be demonstrated in the effluent. The material retained by the column was then eluted with 0.2 molar sodium chloride and precipitated from the eluate by saturation with sodium chloride. The yield of salt cake was about 2 g from 5 g of the methanol-extracted starting material.

The salt cake was dissolved in 0.5% sodium chloride solution to a 3% solution. Three volumes of ethanol were added at room temperature and the precipitate that formed was filtered off and discarded. To the filtrate were added two volumes of n-butanol precooled to −15 C. The precipitate that formed was filtered off, washed on the funnel with butanol and ether, and then air-dried. The yield was about 1 g per 2 g sodium chloride precipitated material.

Further purification was achieved in using a column of triethyl-aminoethyl cellulose, equilibrated with a sodium pyrophosphate-orthophosphoric acid buffer, containing N, N'dimethyl formamide.* The cholecystokinin-pancreozymin was dissolved in this buffer to a 5% solution and the pH of the solution adjusted to 9.1 with a solution made by adding

* $Na_4P_2O_7 \cdot 10\,H_2O$ 2.33 g + 1 ml 1 M H_3PO_4 in a volume of 1 liter. The pH of this solution should be adjusted to 9.1, if necessary, electrometrically with hydrochloric acid or sodium hydroxide. Nineteen parts by volume of this solution and one part N, N' dimethyl formamide.

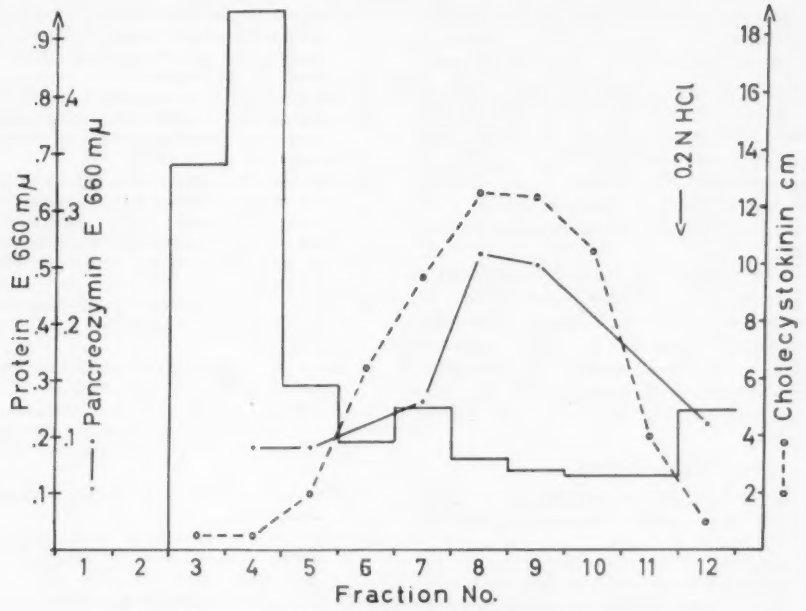


FIGURE 3. Chromatographic purification of cholecystokinin-pancreozymin on a triethyl-aminoethyl cellulose column.

one part by volume of dimethyl formamide to 19 parts 0.02 molar sodium hydroxide. A volume containing 0.5 g was passed into the triethyl-aminoethyl cellulose-column (3 by 15 cm with 30 g of triethyl-aminoethyl cellulose) and elution commenced with the buffer. Twenty-five milliliters fractional volumes were collected.

The distribution of protein and biological activity as to cholecystokinin and pancreozymin is evident from Figure 3.

It is quite remarkable how closely the two hormone activities follow each other through all these steps of purification including chromatography on a weakly acidic and a strongly basic ion exchanger, the strength of the pancreozymin in the meantime having increased approximately six hundredfold over that of the original standard preparation of Crick, Harper, and Raper. The product is still contaminated with strongly basic proteins as is seen in Figure 1, upper row (A), the activity migrating to the anode.

In view of these findings we can hope shortly to reduce the delay for these gastrointestinal hormones both from the clinical and the chemical points of view.

SUMMARIO IN INTERLINGUA

Esseva elaborate un nove technica pro le preparation del hormones gastrointestinal secretina, cholecystokinina, e pancreozymina ab porcin mucosa duodenal. Le technica consiste essentialmente del sequente manovras: Le enzymas es destruite per disnaturation thermic del proteinas. Le hormones es extrahite con diluite acido acetic, adsorbite ab le extracto ad acido alginic, e purificate additionalmente per fractionation a alcohol, electrophorese a columna de cellulosa, e chromatographia a cellulosas carboxymethylic e triethyl-aminoethylic. Un specimen commercial de secretina pote esser preparate con 75 o 100 unitates clinic per ampulla in circa 0,03 milligramma de substantia lyophilisate. Isto es un puritate circa 1.000 vices plus alte que illo del secretinas previemente fabricate e usate in le practica clinic.

In 1955 le autores succedeva a preparar un cholecystokinina con 22 a 25 unitates canin Ivy

per milligramma. Su activitate pancreozyminic correspondeva a 125 unitates Crick, Harper, e Raper per milligramma. Iste preparato ha essite usate extensemente como adjuvante in le cholecystographia. Un total de 30.000 tal tests ha jam essite effectuate. Post le quadruplice o quintuplice purification additional per medio de chromatographia a cellulosa triethyl-aminoethylic, le activitates de cholecystokinina e de pancreozymina sequeva le un le altere intimemente.

Le autores discute le utilitate de secretina e de cholecystokinina-pancreozymina como instrumentos diagnostic in le gastroenterologia, con referentias particular a recente experientias in le uso de un combinate test a secretina e cholecystokinina-pancreozymina in le diagnose de cancere del pancreas, del vesica biliari, e del vias biliari.

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The Effect of Tolbutamide on Human Basal Gastric Secretion

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THE SUSPICION that a new therapeutic agent may have ulcerogenic potentialities is a matter of great practical concern to the physician. The belief that compounds like the salicylates, steroids, ACTH, and phenylbutazone may induce peptic ulceration by stimulating acid secretion or by diminishing gastroduodenal tissue resistance in susceptible individuals has facilitated the institution of preventive measures, when use of the drug is unavoidable and when the expected benefit warrants the risk involved (1–3).

Up to the present, little has been written in this regard concerning the oral antidiabetic agent, tolbutamide, a sulfonylurea compound with hypoglycemic effects (4–6). In general, few toxic side reactions have been encountered with tolbutamide, despite extensive clinical trials with the drug. C. J. O'Donovan * states that in more than 9,000 diabetics treated with tolbutamide for six to more than 28 months, only 1.53% experienced untoward effects requiring omission of the drug.

Baird and Hull (7) reported a case of cholestatic jaundice with eventual recovery in a diabetic patient undergoing therapy with diet and tolbutamide. Two cases of jaundice, presumably related to tolbutamide, were also cited by Bradley (8). The latter stated that no deaths directly attributable to tolbutamide have occurred, and necropsies of patients who have taken tolbutamide and have died of other causes have failed to demonstrate an organ lesion suggestive of tolbutamide toxicity. He also demonstrated the production of antiplatelet agglutinins by tolbutamide in patients with allergic purpura.

The evidence for the causative relationship of tolbutamide to the cases of fatal myelogenous leukemia reported by Brod (9) and by Mehnert, Camerini-Davalos, and Marble (10) is only remotely suggestive.

Of more immediate interest to the gastroenterologist are the reports of Beaser (11, 12) and of Gelfand (13), encompassing four patients in whom it was felt that tolbutamide was responsible for initiating or reactivating a peptic ulcer.

In 1956 Beaser (11) described his experience with the use of tolbutamide in doses of 2 to 3 grams daily in 35 diabetic patients. He notes, in Case 7 of his series, the occurrence of heartburn following the institution of tolbutamide therapy in a 54-year-old man with diabetes of 14 years' duration. Since no details were given as to the periodicity or food relationship of this symptom, and no X-ray studies were described, the question of the existence of a peptic ulcer remains unanswered. However, in a subsequent report (12) on 90 diabetics receiving doses of 2.5 grams daily, he cautions about gastrointestinal side effects, such as heartburn, abdominal discomfort, and bloating. In addition, he describes two patients, one with a known duodenal ulcer, whose symptoms exacerbated after a period

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of drug ingestion, and the other, a 75-year-old man with no prior history of gastrointestinal disease, who developed a sudden perforation of a duodenal ulcer after 135 days of tolbutamide treatment.

More recently, Gelfand (13) also reported two instances of gastroduodenal bleeding, presumably related to the prolonged ingestion of tolbutamide. Both patients were diabetics with arteriosclerotic heart disease, and had been regulated on 1 to 2 grams of tolbutamide for eight and ten months, respectively. The first patient had a definite history of duodenal ulcer, with numerous recurrences for 15 years, and a positive radiographic diagnosis. The second patient experienced ulcer type dyspepsia for many years, but the barium meal at the time of bleeding disclosed no pathological lesion.

Despite the provocative implication of these reports, the prevalence of peptic ulcer disease in the population at large, with an equally high incidence among diabetics (14), makes it difficult to establish with certainty the suspected causal relationship of this drug to ulceration. A fair appraisal of the ulcerogenic potentiality of tolbutamide necessitates a wide variety of investigative and statistical studies, such as observations of the incidence of ulcer with drug ingestion, the relationship to dosage, the ulcerogenic effect of diabetes mellitus per se, the susceptibility of the individual to ulcer formation, and experimental pharmacological studies in both animals and man. One of the most fruitful techniques in such an analysis is the accurate evaluation of the effect of the drug on the acid-pepsin secretory mechanism, held to be of basic importance in ulcer development. With this end in view, a study was undertaken to determine the effect of intravenous tolbutamide on the unstimulated basal gastric secretion of a group of nondiabetic, nonulcer subjects. Serial blood sugar changes were also recorded to segregate any direct tolbutamide effect from the vagal secretory stimulation incident to the induced hypoglycemia.

Materials and Methods

In order to collect base line data, the investigation comprised a group of 28 subjects, both hospitalized and outpatients, in whom diabetes mellitus and organic disease of the gastrointestinal tract could be reasonably excluded by means of clinical and X-ray examinations. Many patients were being evaluated for gastrointestinal complaints, considered to be of functional origin, after suitable laboratory and X-ray studies. The remainder were undergoing therapy for medical conditions usually unassociated with any effect on the gastric secretory mechanism. Seven patients were excluded from the final evaluation for the following reasons: three patients in whom achlorhydria and low pepsin secretions throughout the period of the test created doubt as to the responsiveness of their secretory apparatus; one patient whose blood sugars disclosed a diabetic type of curve; one patient whose response defied analysis because of complete inhibition of free acid and pepsin secretion during the basal period and the first 40 minutes after the tolbutamide injection, with a sudden rise, at this point, to 50 mEq per liter free hydrochloric acid and pepsin secretion in the 400 unit range; and two patients with whom technical difficulties were experienced, resulting in incomplete collection of samples.

The gastric secretory studies of the remaining 21 subjects, nine males and 12 females, ranging in age from 19 to 68, were considered to be satisfactory for analysis. Fifteen of these 21 subjects were hospitalized patients and six were outpatients.

The subjects were fasted for 12 hours and received no medications for at least 14 hours prior to the test. At 8 AM a Levin tube with radiopaque tip was introduced, through either the nose or the mouth, under fluoroscopic guidance, to the most dependent portion of the

TABLE 1. Mean 15-Minute Volumes, Free and Total Acid Output, pH, and Pepsin Output on All 21 Subjects before and after Intravenous Tolbutamide 1 g

Patient	Age	Sex	Basal Volume ml	Tol-butamide Volume ml	Basal Free Acid Output mEq	Tol-butamide Free Acid Output mEq	Basal Total Acid Output mEq	Tol-butamide Total Acid Output mEq	Basal pH	Tol-butamide pH	Basal Pepsin Units	Tol-butamide Pepsin Units
C. S.	37	F	12.0	17.4	0.11	0.45	0.16	0.76	2.12	1.84	1,488	4,426
G. G.	59	M	12.5	17.9	0.18	0.29	0.44	0.73	2.42	2.48	3,413	4,695
J. W.	34	F	26.3	21.5	0.72	0.49	1.23	0.62	2.10	4.03	6,162	3,077
V. G.	21	M	10.5	18.4	0.36	1.04	0.56	1.57	1.73	1.43	1,016	2,650
M. E.	36	F	20.0	27.1	0.93	1.54	1.42	2.20	1.73	1.53	1,686	2,561
M. C.	32	F	16.9	46.9	0.30	2.45	0.66	3.65	2.21	1.48	2,535	10,580
M. R.	40	F	22.3	25.9	0.31	1.23	0.82	1.76	2.52	1.71	2,558	5,153
F. C.	34	M	10.8	22.1	0.25	0.92	0.50	1.69	1.77	1.43	1,986	4,672
M. H.	68	F	23.3	22.5	0.36	1.03	0.57	1.38	2.56	1.74	5,602	6,334
E. S.	29	M	17.3	26.3	0.77	2.13	0.97	2.68	1.90	1.45	1,257	4,024
J. M.	68	M	10.6	14.3	0.18	0.19	0.21	0.31	2.12	2.00	580	1,276
A. P.	19	M	19.0	30.4	0.67	1.66	0.95	2.19	2.15	1.60	1,809	1,564
A. F.	21	F	17.8	19.3	0.26	0.19	0.47	0.31	1.82	1.95	2,218	871
D. A.	25	F	20.0	39.9	0.44	1.92	0.66	2.50	2.20	1.65	364	368
T. W.	44	M	68.8	75.0	4.10	5.62	5.45	6.91	1.75	1.63	6,851	9,812
J. E.	38	M	19.3	23.1	0.35	1.08	0.77	1.57	1.87	1.50	9,634	12,663
M. P.	46	F	23.8	5.9	0.54	0.58	1.13	0.79	1.92	1.70	6,936	2,804
F. S.	39	F	9.9	14.5	0.31	0.44	0.65	0.90	2.05	1.90	676	1,509
M. P.	19	M	8.5	18.4	0.25	0.50	0.56	1.13	1.66	1.98	1,883	4,187
E. T.	30	F	28.0	27.2	0.34	0.71	0.62	1.06	2.43	2.70	5,684	6,193
D. I.	56	F	39.8	41.7	1.49	1.04	1.69	1.51	1.97	2.20	3,999	6,780
Mean values			20.8	26.7	0.63	1.21	0.98	1.72	2.05	1.88	3,253	4,581
Percentage increase				+26.9		+92.0		+75.6				+40.8

gastric antrum. The patient was then maintained in a sitting position in bed, inclined slightly to the left, and instructed to expectorate all saliva. Attempts were made to isolate and orient the patient adequately, in order to avoid psychic vagal stimulation. The stomach was aspirated as completely as possible of fasting residuum, and this specimen was discarded. The tube was then connected to a suction apparatus regulated to aspirate at a negative pressure of approximately 30 cm of water. The first 30-minute collection was discarded to allow for a settling-down period and adjustment to the tube.

Four 15-minute specimens, comprising the basal secretion, were collected for one hour, and eight 20-minute samples for two hours, after the intravenous injection of 1 g of sodium tolbutamide (Orinase) diagnostic. This preparation has been used in the performance of a supplemental test for the diagnosis of mild diabetes mellitus (15, 16) and for the detection of pancreatic insulinomas (17). In the early phase of the study, the "Mix-o-vial" preparation was used. Subsequently, in compliance with a warning that postinjection thrombophlebitis could result from the use of this preparation, 1 g of Orinase powder, diluted to 20 cm^3 with sterile water, without preservative, was employed. Just prior to the injection of the drug the suction was temporarily discontinued, and a sample of venous blood was drawn for fasting glucose determination. Upon completion of the injection suction was resumed for the post-tolbutamide collections. Each patient, therefore, served as his own control. The tubes were cleared with 5 to 10 ml of air periodically, and hand suction was used at intervals to check completion of sample collections. Serial samples of blood were drawn for glucose determination at the end of each 20-minute post-tolbutamide gastric collection, so as to permit inferences concerning concomitant blood sugar and gastric secretion trends. Each experiment lasted 4 to 5½ hours, and in no instance was termination of the test required because of undue discomfort or intolerance to the tube. Side reactions due to hypoglycemic blood levels were minimal and consisted of slight sweating and mild weakness in a few patients. No severe reactions were encountered.

After the volume of each gastric specimen was measured it was filtered. An aliquot of the filtrate was then titrated for free and total acid, with 0.1 normal sodium hydroxide, using Topfer's reagent and phenolphthalein as indi-

cators; pH values were determined electrometrically with a Beckman meter. Pepsin concentration was measured by the Bucher, Grossman, and Ivy (18) modification of the Anson-Mirsky method (19), using bovine hemoglobin as a substrate. Blood sugar determinations were made by the Folin-Wu method.

The laboratory data on the 20-minute post-tolbutamide specimens were prorated into 15-minute averages, for purposes of comparison with the basal samples. Fifteen-minute outputs of free and total acid and pepsin were calculated from the concentrations and volumes.

Results

The gastric secretory responses obtained in each of the 21 subjects after the injection of tolbutamide, as compared with his basal secretion, are shown in Table 1. The values are tabulated as averages per 15-minute intervals, the volumes in milliliters, the acid output in milliequivalents, and pepsin, in units (19). The calculated mean values for all variables in the entire group of 21 subjects, before and after drug administration, are given below the list of subjects.

It will be noted that an increase in mean volume was observed from 20.8 to 26.4 milliliters, a rise of 26.9%. A significance test of t value, applied to these results, indicates that a statistically significant difference exists between the control and post drug volumes ($t^2 = 8.10$, $P = 0.01$) (21).

The most marked increase occurred in the free acid output which rose 92% from a basal value of 0.63 mEq per 15 minutes to 1.21 mEq after tolbutamide. This represents a highly significant increase at the 1% level ($t^2 = 15.9$, $P = 0.01$) (21).

The mean total acid output increased 75.6%, from 0.98 to 1.72 mEq per 15-minute interval, also highly significant at the 1% level ($t^2 = 17.2$) (21). The greater proportionate increase in free and total acid output as compared to volume reflects the marked effect on the concentration of acid. The drop in pH values also demonstrates the stimulant effect on acid secretion. The observed rise in pepsin output from 3,253 to 4,581 units (+40.8%) was not as striking as the rise in acid output, but was still considerable and statistically significant at the 5% level ($t^2 = 6.8$, $P = 0.05$).

Table 1 also demonstrates the widely varying range of response encountered in this group of 21 subjects. For example, M. C. increased her 15-minute basal volume from 16.9 to 46.9 milliliters (+177.5%). On the other hand, in A. F. the 15-minute volume rose from 17.8 to 19.3 milliliters (+8.4%), hardly significant in terms of a variable function such as gastric secretion. T. W., a hypersecretor, with negative X-ray findings and with a basal volume of 68.8 ml per 15 minutes, showed a minimal increase of only 6.2 milliliters (+9%). In view of the latter's high basal volume, this is proportionately an even smaller increase than that of A. F.

The response in free acid output also varied from a maximal increase of 716% over the basal output (M. C.) to a negligible rise of 5.5% (J. M.).

TABLE 2. Proportion of 21 Subjects Showing a Rise, Fall, or no Significant Change of Basal Secretion in Volume, Free and Total Acid, pH, and Pepsin Output Following Administration of Tolbutamide

	Volume		Free Acid Output		Total Acid Output		pH		Pepsin Output	
Type of Change	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Increase	15	71.5	16	76.2	17	80.9	4	19.1	15	71.5
Decrease	2	9.5	2	9.5	4	19.1	12	57.1	4	19.1
No significant change < 10 per cent	4	19.1	3	14.3	0	0.0	5	23.8	2	9.5

TABLE 3. Record of M. R., Female, Age 40, Showing Effect of 1 g Tolbutamide Intravenously on Volume, Concentrations of Free and Total Acid and Pepsin of Basal Gastric Secretion. Blood Sugar Response Curve, See Figure 1

Time Interval		Volume ml	Free Acid Concentration mEq per liter	Total Acid Concentration mEq per liter	pH	Pepsin Units per ml
Basal	15	11.0	10	40	3.8	105
	30	20.0	12	35	2.3	110
	45	8.0	18	40	2.1	120
	60	50.0	15	30	1.9	122
Mean value		22.3	13.8	36.3	2.52	114.3
Tolbutamide	15	15.0	14	26	2.4	143
	30	11.0	13	26	2.3	141
	45	18.5	19	32	2.2	146
	60	37.5	31	44	1.5	150
	75	26.0	56	69	1.4	164
	90	32.0	55	74	1.35	157
	105	34.0	52	72	1.35	151
	120	33.0	43	64	1.5	142
Mean value		25.9	35.4	50.9	1.71	149.2

The range of increase in total acid output varied from a low of 27% (T. W.) to the maximum of 453% (M. C.), and that of pepsin, from 8.6% (E. T.) to 317% (M. C.).

Table 2 demonstrates the percentage of the 21 subjects tested who showed an increase, a decrease, or no significant change (less than 10% increase or decrease) in the determined variables of gastric secretion. It will be seen that over 70% of the patients revealed significant rises in the volume, free and total acid, and pepsin, after receiving 1 gram of tolbutamide. The remainder showed either a decrease or no significant change.

As seen in Table 1, a high degree of parallelism of post-tolbutamide acid and pepsin secretions was exhibited by this group of subjects. Of the total, 18 (86%) responded with a concomitant rise or fall in both variables. Fifteen of these showed an increase in the parietal and peptic components while in the remaining three subjects of this group the acid and pepsin values declined.

Three subjects of the total group (14%) showed a lack of correspondence in the acid and pepsin secretions. In two of these instances, the acid values rose, whereas the pepsin enzyme decreased in one and was unchanged in the other. The third subject of this small group demonstrated a decrease in acid and a rise in pepsin.

Table 3 is the record of a 40-year-old female (M. R.) demonstrating the typical result from a single experiment, suggesting a stimulatory effect of tolbutamide on the gastric secretory mechanism. This study indicates a pronounced rise in the basal free acid concentration, from a mean of 13.8 to 35.4 mEq per liter per 15-minute sample (+156%), and in the total acid concentration, from 36.3 to 50.9 mEq per liter (+42%). Gastric pepsin concentration increased moderately, from a mean of 114.3 to 149.2 units per ml (+30.5%). The volume response was small, from 223 to 259 ml per 15 minutes (+16.1%). The marked hydrogen ion increase is indicated by the drop in pH from 2.52 to 1.71. Figure 1 illustrates the concomitant blood sugar response to the injection of 1 gram tolbutamide intravenously in the same patient.

The maximal fall in blood sugar was attained in 40 minutes, from a pre-drug level of 90 to a low of 60 mg per 100 ml, a decline of 33% from the pre-test value. Comparison with Table 3 suggests that, although a slight rise in volume and in free and total acid concentration, and a drop in pH was developing in the early phase of the post-tolbutamide period, it became more marked after the maximal blood sugar drop. During the subsequent rise in the blood sugar to the pre-injection level there was continued outpouring of large volumes of gastric juice, with high acid and pepsin concentrations for approximately 50 minutes after the peak tolbutamide action, finally reaching a volume of 34 milliliters 55 mEq per liter, free acid concentration, 74 mEq per liter total acid concentration, pH 1.55, and 157 pepsin units per ml. In the final 30-minute period, after the normal fasting blood sugar had been reestablished, the gastric secretory values started to return toward basal levels. In general, the rate of secretory response among those subjects demonstrating a rise in the acid and pepsin components after tolbutamide was similar to that in subject M. R., the maximal increase occurring after the initial 30 to 45 minutes had elapsed.

In order to determine the chronological relationship of the tolbutamide secretory stimulant response to the time of maximal hypoglycemic effect, a graph was constructed, superimposing the average serial blood sugar curve on the pre-tolbutamide and post-tolbutamide secretory values, with each 15-minute sample averaged for all 21 experiments (Figures 2 and 3). On the ordinates are shown the volume, free and total acid, and pepsin output to the left, and the blood glucose to the right; while on the abscissae are indicated the 15-minute time intervals. The vertical bar represents the time of drug injection.

It will be seen from Figure 2 that the maximal mean volume and free acid output responses of 31.7 milliliters and 1.382 milliequivalents, respectively, were attained approximately 75 minutes following the injection of tolbutamide, and 35 minutes after the lowest blood sugar level of 62.6 mg per 100 ml had been reached. The stimulant effect on the volume and hydrochloric acid secretion began approximately 15 minutes after administration of the

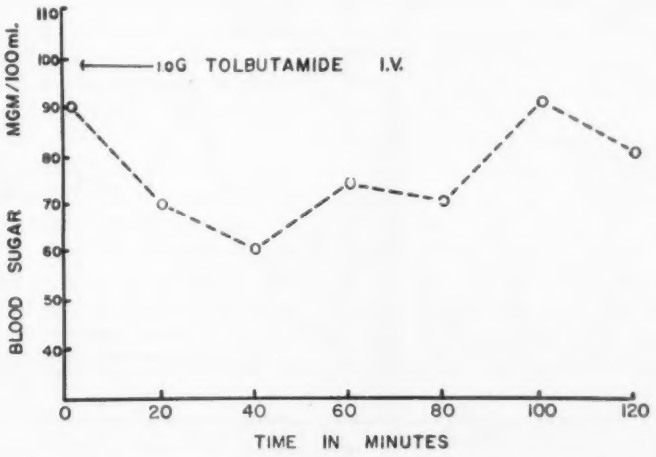


FIGURE 1. Intravenous tolbutamide response curve in M. R. following 1 g sodium tolbutamide intravenously.

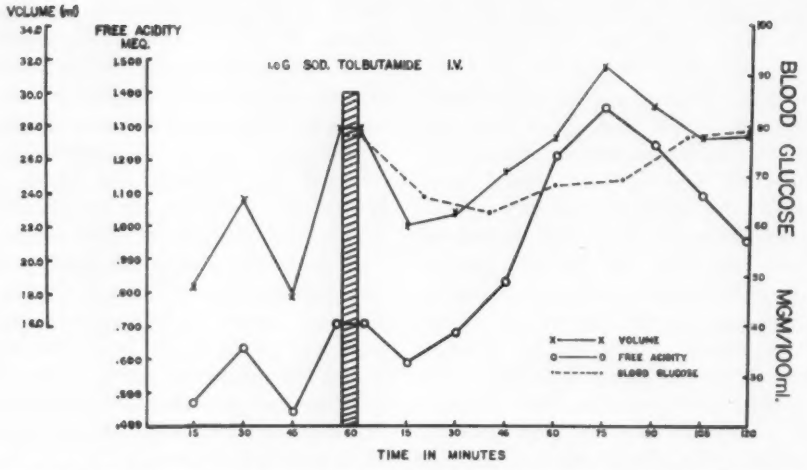


FIGURE 2. Blood glucose tolbutamide response curve superimposed on average volume and free acid output for each 15-minute interval before and after drug injection (21 subjects).

drug, as the blood glucose was declining. Conversely, the descent of the secretory response from its peak level at 75 minutes occurred pari passu, with the return of the blood sugar to its pre-drug level. Since the experiments were terminated two hours after the tolbutamide was given, the precise duration of the secretagogue action remains unknown.

Figure 3 demonstrates a similar inverse relationship between the hypoglycemic effect of tolbutamide and the total acid and pepsin output, which rose to maximal mean values of 1.810 milliequivalents and 4,575 units, respectively. The peak pepsin response was obtained somewhat earlier than the maximal effect on total acidity, that is, within 60 minutes for the former, as com-

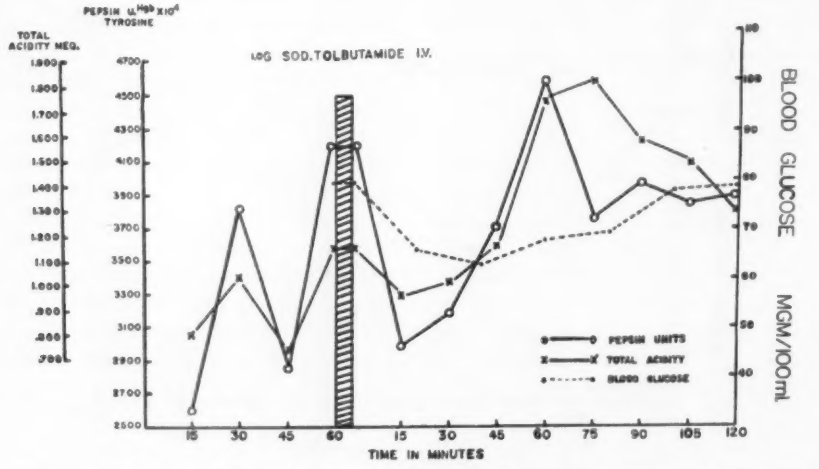


FIGURE 3. Blood glucose tolbutamide response curve superimposed on average total acid and pepsin output for each 15-minute interval before and after drug injection (21 subjects).

pared with 75 minutes for the latter. The tendency for the pepsin and total acidity to return to the original pre-drug values, during the last 45 to 60 minutes of the experiment when the blood sugar was rising, resembled the effect on volume and free acidity.

Calculation of the average serial 20-minute blood sugar levels of our 21 subjects showed that 1 gram of intravenous sodium tolbutamide produced a rapid fall in the blood sugar for approximately 40 minutes, followed by a secondary rise for 80 minutes, finally attaining the initial pre-drug level. The recorded mean values after the drug injection were as follows: fasting, 78.6 milligrams; 20 minutes, 65.5; 40 minutes, 62.6; one hour, 67.8; one hour and 20 minutes, 68.9; one hour and 40 minutes, 77.1; and two hours, 78.1. The maximal drop was 21% of the pre-injection level. As no blood specimen was drawn at the 30-minute period, the very lowest blood sugar attained may have been missed.

Discussion

The current study indicates that tolbutamide is capable of exerting a secretagogue action on the parietal and pepsin components of basal gastric secretion in nonulcer subjects. The effect is variable in duration and degree in different individuals. In a small percentage of patients, in fact, a slight inhibitory effect is produced.

Our experimental results also suggest that the stimulant effect is secondary to the blood sugar depression characteristic of tolbutamide action. There is, in fact, a striking resemblance between our Figures 2 and 3, demonstrating this relationship, and the graph published by Stempien, French, Dagrade, Movius, and Porter (22), illustrating the acid secretory response to hypoglycemia induced by 15 units of insulin given intravenously. They demonstrated a tenfold increase in free hydrochloric acid output following the drug injection with a return to basal levels as the blood sugar rose. Although the magnitude of the decline of the blood glucose in their investigation was more impressive, the general effect on the acid secreting mechanism is qualitatively similar. Their data would suggest that insulin is a much more potent secretagogue than tolbutamide. This is not surprising when one considers the feeble hypoglycemic effect of the usual dose of tolbutamide which is readily duplicated by 2 to 4 units of insulin.

The inference may be drawn from our data, therefore, that the augmentative effect of tolbutamide on gastric secretion is an indirect one, acting through the hypothalamic-vagal pathways initiated by the hypoglycemic stimulus. Further work is necessary, however, to test this hypothesis with a challenging dose of tolbutamide administered to the experimental animal in whom a vagally denervated gastric pouch has been constructed. Additional experimental investigations are indicated to explore the effect of both oral and intravenous tolbutamide on the basal and stimulated gastric secretion of ulcer subjects and diabetic patients. Also, carefully controlled statistical studies are required to analyze the incidence of peptic ulcer in large groups of patients under therapy with the drug for varying periods of time. Local gastric irritative effects of the drug may be investigated by gastroscopic observations or by fecal occult blood studies. Until such time as more positive evidence of the ulcerogenic action of tolbutamide can be presented, no unusual precaution is deemed to be necessary in the clinical use of the drug for diabetes mellitus.

It is believed that the data in the present report do not support the thesis of any direct specific effect of tolbutamide on the parietal or peptic cell secretions.

Summary and Conclusions

1. The administration of tolbutamide to 21 nondiabetic, nonulcer subjects produced

a significant and moderately prolonged increase of basal gastric secretion in 71.4% of the group with regard to volume, pepsin, and free and total acid output. The remaining 28.6% of the experimental subjects responded with no significant change or with an inhibitory effect. In 86% of the experiments, the acid and pepsin components showed a parallel rise or fall.

2. The most marked stimulation of secretion was obtained in the concentration and output of free hydrochloric acid.

3. The total duration of the stimulatory effect of tolbutamide was not seen, but is estimated to last approximately two to three hours.

4. The initial rise and subsequent fall of the components of basal gastric secretion were found to correlate with the hypoglycemic response to tolbutamide. Consequently, a central vagal pathway, rather than a direct parietal cell effect is postulated.

5. Additional work is necessary for a more precise definition of the effect of tolbutamide on the gastric secretory mechanism of diabetic and peptic ulcer patients. Accurate, well controlled, statistical studies on patients treated with tolbutamide are needed to establish any significant ulcerogenic potentiality.

Acknowledgment

The authors wish to express their thanks to the Upjohn Company, Kalamazoo, Michigan, for the research grant and the generous supply of sodium tolbutamide; to Dr. Charles Cramer, Director of the Department of Internal Medicine, for permission to conduct the investigation on the medical wards of Flushing Hospital and Dispensary; and to Levan Johnson, biochemist, for his invaluable technical assistance, under the direction of Dr. Irene Garrow, pathologist.

Summario in Interlingua

Disperse reportos in le litteratura suggere que tolbutamida exerce possibilemente un effecto ulcerogene in susceptibile subjectos, con le resultato de sanguination e perforation gastrointestinal.

Le autores ha interprendite un studio experimental in 21 subjectos normal pro determinar le effecto de 1 gramma de tolbutamida intravenose super le secretion gastric per comparar le valores de base pro le rendimento de 15 minutas in volumine secretori, acido, e pepsina con le correspondente valores obtenite post le administration de tolbutamida. Analyses del sucro de sanguine esseva facite simultaneemente con le collectiones gastric durante le periodo post le administration de tolbutamida pro determinar si forsan un effecto de stimulation gastric poteva esser relationate con le inducite hypoglycemia.

Le datos demonstrava que tolbutamida produceva un statisticamente significative effecto stimulatori in le secretion de acido e de pepsina e que iste effecto durava approximativemente duo a tres horas.

Le augmentos del valores pro le diverse parametros del secretion gastric post le administration de tolbutamida esseva: Volumine medie del secretion in 15 minutas, ab 20,8 ad 26.7 millilitros (i.e. + 26,9%); rendimento de acido libere, ab 0,63 ad 1,21 milliequivalentes (i.e. + 92%); rendimento de acido total, ab 0,98 ad 1,72 milliequivalentes (i.e. + 75,6%); e rendimento de pepsina, ab 3.253 ad 4.581 unitates (i.e. + 48,8%).

Inter le 21 subjectos, plus que 71% exhibiva un responsa stimulatori a tolbutamida. In le alteres, nulle effecto o un leve depression esseva constatate. Le componentes acido e pepsina esseva in parallela in montar o declinar in 86% del subjectos experimental.

Viste que le responsa de stimulation gastric post tolbutamida occurreva durante que le sucro de sanguine declinava, un action hypothalamicovagal es postulate plus tosto que un directe effecto super le pariete cellular.

Es concludite que le presente studio non supporta le idea de un directe action ulcerogenic de tolbutamida. Studios additional es proponite pro explorar le mentionate possibilitate in plus grande detalio.

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Acute Fatty Metamorphosis of the Liver

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FATTY METAMORPHOSIS OF THE LIVER is a common finding in autopsy or liver biopsy material obtained from patients with a history of severe alcoholism (1–4). In some instances, fatty liver is not associated with clinical manifestations of liver disease. In other cases, fatty metamorphosis may be of such severity as to be associated with acute signs and symptoms. In 1836 Addison (5) noted that most of the patients with fatty liver that he observed were addicted to alcohol. Most of the subsequent clinical reports of fatty liver have been intermingled with cases of Laennec's cirrhosis, and as a result a clearly delineated clinical picture has, for the most part, been lacking.

Although some of the signs and symptoms of acute fatty metamorphosis coincide with those of typical Laennec's cirrhosis, it has been our experience that there is in most cases a quantitative difference and frequently a qualitative difference between the two. Acute fatty liver syndromes may be superimposed upon an underlying cirrhosis. It is the purpose of this paper to describe the clinical aspects of acute fatty metamorphosis of the liver with and without associated cirrhosis based on 40 histologically proven cases seen at the Philadelphia General Hospital. The emphasis will be placed on differential diagnosis, and an attempt will be made to correlate the clinical manifestations with the degree of fatty changes and fibrosis in the liver.

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METHOD OF STUDY

Forty cases were selected for analysis. The records from 1938 to 1958 were studied of all cases with a pathological diagnosis of fatty liver, fatty dystrophy, fatty infiltration, fatty metamorphosis, fatty cirrhosis, and fatty degeneration. Those patients whose predominant clinical manifestations were not considered to be related to their liver disease were eliminated. In addition, those cases in which the fatty liver was related to a specific hepatotoxin, such as carbon tetrachloride and phosphorus, were not included.

All histologic sections of the livers were studied. Sections stained with hematoxylin and eosin and with trichrome were available in every case. Since specific staining for fat was not available in a majority of the cases, the following grading was based on the hematoxylin and eosin and trichrome stained sections. The liver sections were graded as follows:

Grades 0 to 4 + with regard to fat vacuolization:

Grade 0 = No vacuoles.
Grade 1 + = Slight vacuolization (intracellular).
Grade 2 + = Moderate vacuolization (mostly intracellular).
Grade 3 + = Marked vacuolization (intracellular and extracellular).
Grade 4 + = Severe vacuolization (intracellular and extracellular with formation of fatty cysts).

Grades 0 to 4 + with regard to fibrosis:

Grade 0 = No increased fibrosis.
Grade 1 + = Minimal increase in portal fibrous tissue.
Grade 2 + = Moderate increase in portal fibrous tissue but without fibrous septa.
Grade 3 + = Moderate to marked increase in portal fibrous tissue plus definite formation of fibrous septa.
Grade 4 + = Severe fibrosis with marked septa formation and marked lobular distortion.

The cases were then divided into two subgroups based on the above grading. Cases with 0, 1 +, or 2 + fat were eliminated. Cases with 3 + or 4 + fat and 0, 1 +, or 2 + fibrosis were classified as having *fatty metamorphosis* (Group I). Cases with 3 + or 4 + fat and 3 + or 4 + fibrosis were classified as having *fatty cirrhosis* (Group II).

There were 29 patients in Group I and 11 in Group II. There were 25 autopsied cases and 15 cases diagnosed by liver biopsy (14 with a Vim-Silverman needle percutaneously and one with an open surgical biopsy). In almost every case routine blood counts, urinalyses, blood urea nitrogen, blood sugar determinations, and several liver function tests were obtained. Other clinical studies and X-ray examinations were done as indicated.

CLINICAL DATA

Age Distribution, Sex, and Race: The mean age of the entire group of 40 patients was 42 years, with a range of 23 to 68 years. However, the peak age incidence of Group I (fatty metamorphosis, 41%) was in the fourth decade, while 54% of the patients in Group II (fatty cirrhosis) were in the fifth decade of life.

The composition of the entire group with regard to sex was similar to the composition of the hospital population (60% males and 40% females). On the other hand, there was a definite preponderance of Caucasians (65%) compared to the general hospital population in which 48% were Caucasians and 52% were Negroes.

Among those patients who died, there was a relatively greater proportion of females (50%) and Caucasians (78%) than in the entire group of 40 patients.

Predisposing Factors (Alcohol and Diet): In all cases in which accurate historical data were available, there was a history of ingestion of large amounts of alcoholic beverages. It was impossible to obtain an accurate breakdown of the types of beverages ingested, although most of the patients were heavy whiskey or wine drinkers. In the majority of patients, a recent marked increase in the quantity of alcohol consumed associated with a grossly inadequate dietary intake of foods high in protein and vitamin content preceded hospitalization.

Incidence of Various Clinical Manifestations (Figure 1): Hepatomegaly was the most common clinical manifestation in both subgroups. The surface of the liver was usually described as being smooth with a rounded edge. Hepatic tenderness was much more prominent in the fatty metamorphosis group than in the fatty cirrhosis group, and in several patients the tenderness was as severe as that seen in some cases of viral hepatitis or acute hepatic congestion. Clinical jaundice was present in one-half of all patients. It was of greater intensity in patients with fatty cirrhosis. Pruritus was not common. Psychopathy, when present, included toxic psychosis, disorientation, aggressiveness, negativism, and hostility.

Abdominal pain was much more common in Group I than in Group II. It was localized to the right upper quadrant in three cases, was epigastric in six, was periumbilical in one, and was vague or diffuse in the remaining cases. Nausea and vomiting were associated with the pain in 30% of the cases.

Shock and dyspnea of sudden onset were

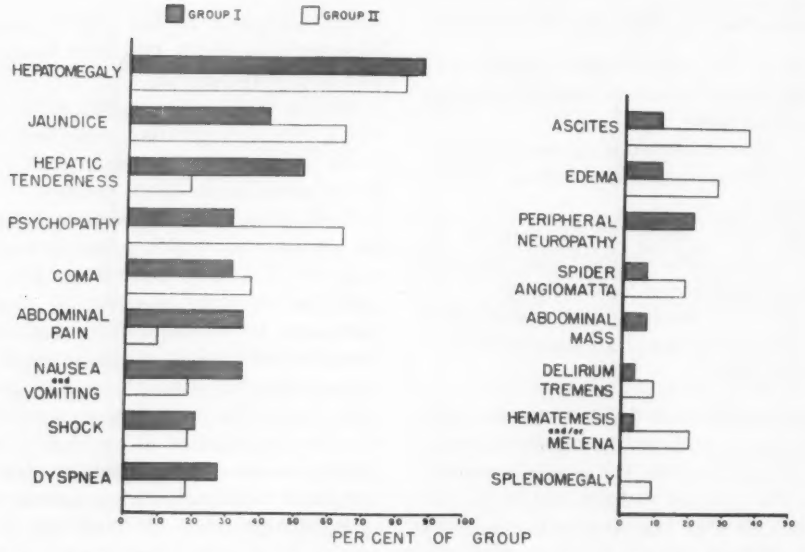


FIGURE 1. Incidence of various clinical manifestations in Group I (fatty metamorphosis) and Group II (fatty cirrhosis).

two important manifestations. In only two of eight patients with sudden onset of peripheral vascular collapse could this finding be explained by hemorrhage. In five instances the sudden onset of dyspnea, tachypnea, tachycardia, feeble pulse, sweating, and profound hypotension requiring pressor agents occurred simultaneously. Four of these patients had simple fatty metamorphosis and one had fatty cirrhosis. No cause for these acute clinical manifestations could be found at autopsy.

Ascites, peripheral edema, spider angiomata, splenomegaly, and esophageal varices were present in less than 20% of all cases, occurring more frequently in the fatty cirrhosis group (Group II). Massive hemorrhage into the gastrointestinal tract was noted clinically in three cases. One patient in Group I had erosive gastritis and two in Group II had ruptured esophageal varices. In two patients the major clinical manifestation was an undiagnosed abdominal mass; this remained a diagnostic problem until needle biopsy revealed a fatty liver, and the mass subsided during hospitalization.

Grouping of Principal Presenting Manifestations: Aside from hepatic coma, shock, and dyspnea, which were associated with rapid demise, jaundice, hepatomegaly, abdominal pain, and hepatic tenderness were the most common clinical manifestations in the over-all group and occurred in several possible combinations. Table 1 arranges these four manifestations in groups according to their occurrence when the patients were first admitted to the hospital, in order to illustrate the potential problems in differential diagnosis. It will be noted that six patients in Group I were admitted to the hospital with severe abdominal pain not associated with clinical jaundice, and the most significant physical sign was a large and tender liver. In ten patients only painless jaundice and hepatomegaly were present; the liver was not tender. However, in six of these ten patients encephalopathy was present, which could have masked pain or tenderness.

Mode of Death (*Figure 2*): Twenty-six patients had a fulminating clinical course and died shortly after admission to the hospital. Half of the patients who died in both subgroups manifested hepatic coma. Pneumonia was an important contributing factor in three patients. Nine patients in Group I and four in Group II died suddenly with severe dyspnea and peripheral vascular collapse. At autopsy the cause for these signs and symptoms could be explained by gastrointestinal hemorrhage in only four patients. Two patients with erosive gastritis were in Group I, and two patients with ruptured esophageal varices were in Group II. In the remaining nine patients there was no evidence of hemorrhage, myocardial infarction, pulmonary embolus, or adrenal disease. In some of these patients a history of one or more transient episodes of acute dyspnea during the year preceding hospitalization was obtained.

Differential Diagnosis: Of the various diseases listed on the chart as provisional diagnoses, fatty liver was mentioned in only four instances. Laennec's cirrhosis was the most common clinical impression. Toxic or infectious hepatitis was considered in seven cases. In four cases, acute cholecystitis or choledocholithiasis were important diagnostic considerations. In 11 patients various diagnoses such as gastritis, pancreatitis,

TABLE 1. Grouping of Principal Presenting Manifestations *

Presenting Manifestations	Number of Patients		
	Group I	Group II	Total
Abdominal pain, jaundice, hepatomegaly, hepatic tenderness	4	1	5
Abdominal pain, hepatomegaly, hepatic tenderness (no jaundice)	6	0	6
Jaundice, hepatomegaly, hepatic tenderness (no spontaneous pain)	2	2	4
Jaundice, hepatomegaly (no pain or tenderness)	4	6	10

* Includes those patients in whom two or more of the signs or symptoms listed were initially present as the most prominent manifestations.



FIGURE 2. Mode of death in 26 patients. The ordinate indicates the percentage of patients who died in Group I (fatty metamorphosis) or Group II (fatty cirrhosis), who exhibited the manifestations indicated on the abscissa.

TABLE 2. Laboratory Data—Groups I and II

Determination	Upper or Lower Value Accepted as Normal	Group I				Group II			
		Number*	Mean	Range	% Less (L) or Greater (G) Than Normal	Number*	Mean	Range	% Less (L) or Greater (G) Than Normal
Hemoglobin	11 g/100 ml†	25	11.3	6.4–18.2	40 (L)	9	10.4	3.1–13.9	44 (L)
WBC count	10,000/mm³†	24	8,900	4,600–19,600	25 (G)	10	9,400	4,500–18,100	40 (G)
Serum albumin	3.5 g/100 ml‡	17	4.2	2.3–7.2	35 (L)	10	2.9	2.0–3.9	70 (L)
Serum globulin	3.5 g/100 ml†	16	2.2	0.8–3.2	0 (G)	10	3.7	2.3–4.9	60 (G)
Serum alkaline phosphatase	5 Bodansky units†	10	4.2	1.0–10.2	20 (G)	7	4.5	1.5–8.2	29 (G)
Serum cholesterol	275 mg/100 ml†	13	256	132–473	30 (G)	7	207	133–463	14 (G)
Cholesterol esters	50%‡	12	48	27–81	50 (L)	5	24	5–38	100 (L)
Thymol turbidity	5 units†	18	2.4	0–7.5	6 (G)	7	6.0	0–11.8	57 (G)
Thymol flocculation	2+†	17	—	0–2+	0 (G)	7	—	0–4+	29 (G)
Cephalin flocculation	2+†	19	—	0–4+	47 (G)	8	—	1+–4+	87 (G)
Prothrombin time	50%‡	16	52	33–98	44 (L)	6	41	23–76	83 (L)
Bromsulfalein retention	10%†	13	27	9–60	85 (G)	3	26	14–32	100 (G)
SGO-T	60 units†	2	216	—	100 (G)	2	196	—	100 (G)
Serum bilirubin: total	1.5 mg/100 ml†	16	2.96	0.16–10.8	44 (G)	8	11.02	0.20–25.30	88 (G)
"one-minute"	0.8 mg/100 ml†	6	1.61	0.20–4.10	17 (G)	3	10.33	4.60–13.70	100 (G)

* Number in whom study was made.
† Upper limit of normal.
‡ Lower limit of normal.

peptic ulcer, hiatal hernia, metastatic carcinoma, and acute pulmonary edema with congestive heart failure were considered.

LABORATORY DATA (TABLE 2)

Anemia, usually of moderate degree, was present in both subgroups, but was more severe in those with fatty cirrhosis. In most cases it was normochromic and normocytic, but slight to moderate macrocytosis was found, and target cells were frequently noted. There was no relationship between the anemia and hypercholesterolemia. Leukocytosis was present in 25% of Group I and 40% of Group II, but it was not necessarily associated with infection. In three cases with pneumonia, two had a white blood cell count of 10,000/mm^3 or less, and the third had a white blood cell count of 19,600/mm^3.

The laboratory tests indicative of hepatocellular function tended to show quantitative differences between simple fatty metamorphosis and fatty cirrhosis. In the former the mean levels of albumin and globulin and the albumin-globulin ratio were within normal limits, while hypoalbuminemia and hyperglobulinemia characterized the latter as compared to Group I. The flocculation tests, prothrombin time, and cholesterol ester determinations also showed greater abnormality in Group II than in Group I. The bromsulfalein test was the most consistently abnormal test in the entire 40 patients, with 90% of the cases having a retention of over 10% in 30 minutes. Those with normal bromsulfalein retention were in Group I.

In six patients (four with fatty metamorphosis and two with fatty cirrhosis) either the total serum cholesterol or the alkaline phosphatase level, or both, were elevated in association with an increased serum total bilirubin level suggesting obstructive jaundice. In none of the five patients with hypercholesterolemia was severe anemia (hemoglobin less than 11 g/100 ml) present. The patients in Group II had chemical jaundice more often than those in Group I, and the bilirubin rose to much higher values in these patients. In two patients in Group II the total serum bilirubin value was greater than 25 mg/100 ml and the one minute bilirubin values were greater than 12 mg/100 ml. The serum glutamic oxaloacetic transaminase (SGO-T) level was determined in four patients. The values were only moderately elevated.

RESPONSE TO THERAPY

In most patients a high calorie, high protein diet was prescribed. In recent years cases with impending hepatic coma were initially placed on a restricted protein intake with gradual increase in protein as their condition improved. Antibiotics, enemas, cathartics, and blood transfusions were added to the therapeutic regimen as required. Many patients were empirically given supplementary vitamins (B-complex, C, K), liver extract, and lipotropic agents, such as choline chloride. An initial period of bed rest was usually instituted. Those who responded to therapy manifested progressive improvement in appetite, clearing of the sensorium, decreasing jaundice, loss of liver tenderness, and regression of the size of the liver. The patients in Group I who recovered had nearly normal bromsulfalein retention. Patients in Group II showed improvement in most liver studies but often showed persistent abnormalities in at least some of the determinations such as the flocculation tests, serum globulin, and the bromsulfalein test. Those who were discharged had been in the hospital from two weeks to three months, with an average length of stay of four weeks.

DISCUSSION

In experimental animals it has been shown that fatty metamorphosis of the liver can result from deficiency of choline (6, 7) and can be prevented by betaine, vitamin B_{12}, folic acid-citrovorum factor and me-

thionine (8, 9). These lipotropic agents aid fat transport from the liver via phospholipids or by increasing the cellular oxidation of fat. Deficiency of lipotropic substances may be absolute or relative—i.e., relative in that dietary fat or total caloric intake is greater than proportionate protein intake containing necessary lipotropic substances. Thus it is possible to produce fatty liver by nutritional imbalance as well as by deficiency of specific factors. This concept has been emphasized by Popper and Schaffner (8, 10).

In man, fatty metamorphosis of the liver may be seen in a variety of clinical settings (3, 11) such as intoxications (carbon tetrachloride, phosphorus), endocrinopathies such as diabetes mellitus (12), chronic hepatic congestion, anemia, obesity, alcoholism, and malnutrition (kwashiorkor or intestinal malabsorption). In the United States fatty liver is seen commonly in the alcoholic. Here the circumstances leading to nutritional imbalance are most pronounced. It has been estimated that the chronic alcoholic consumes from 2,000 to 4,000 calories daily in the form of alcohol (13). The combination of increased demand for lipotropic agents plus decreased intake of biologically adequate protein sets the stage for the development of fatty metamorphosis (1).

The sequence of pathologic changes in the development of experimental fatty liver has been summarized by Hartroft (7). In the early stages there is an intracellular accumulation of fat. In time the cells become greatly distended with lipid and finally rupture. The extracellular fat coalesces to form fatty cysts. Serial liver biopsies in patients developing fatty livers (1) demonstrated intracellular and extracellular accumulation of fat with conglobation of intracellular fat to produce large globules displacing the cell nucleus.

The development of marked fatty metamorphosis of the liver in man may be associated with an acute clinical syndrome (1, 3, 8, 13–18). Compared to Laennec's cirrhosis, fatty liver occurs in a younger age group (3). Thus, in the present series the mean age for the entire 40 patients was 42 years, and the peak incidence in patients with simple fatty metamorphosis occurred in the fourth decade (41%). The age incidence in the fatty cirrhosis group reached a peak of 54% in the fifth decade of life. This can be compared to a series of 200 cases of cirrhosis (19) in which most patients were in the fifth to sixth decades (average, 50.4 years), to a series of 243 autopsied cases of cirrhosis studied at Philadelphia General Hospital in 1936 where most of the patients were in the sixth to seventh decades (20), and to a series of 782 autopsied cases of cirrhosis (13) in which 49% of the cases were between 40 and 60 years of age.

In our over-all group of patients 60% were males and 65% were Caucasians. The sex incidence can be explained by the composition of the patient population of Philadelphia General Hospital. However, the predominance of white patients does not correspond to the statistics in the hospital population, which is one-half white and one-half Negro. Popper and Szanto (3) found a large predominance of whites and a slight predominance of females among their cases of large fatty liver, and a much greater incidence of males in their cases of fatty cirrhosis. Our cases tended to point to a poorer prognosis in whites than in Negroes and in females than in males, although the numbers were not large enough to be conclusive.

The most important clinical manifestations of acute fatty metamorphosis from a diagnostic point of view are hepatomegaly (often marked), jaundice, abdominal pain, liver tenderness, shock, and dyspnea. The hepatomegaly is due chiefly to massive accumulation of fat in the liver. In those with predominantly fatty changes and little fibrosis the consistency of the liver was softer than in those with fatty changes super-

imposed upon an underlying cirrhosis. Jaundice occurred in both subgroups, but it was more frequent and more severe in those with fatty cirrhosis. The presence of pre-existing chronic disease in Group II may have been a factor here. Popper and Szanto (3) and Koch-Weser, Farber, and Popper (21) have suggested that jaundice in cases with fatty livers may be the result of intrahepatic cholestasis. This could explain the associated findings of hypercholesterolemia, elevated serum alkaline phosphatase, or both, which were observed in six patients.

Both the abdominal pain and the liver tenderness may be related to the rapidity and severity of fat accumulation. Thus, rapid enlargement of the liver can stretch the capsule of Glisson and produce pain and tenderness similar to that seen in acute right-sided congestive heart failure with hepatic congestion. It is interesting that the fatty cirrhosis group had a much lower incidence of pain and tenderness than the fatty metamorphosis group. Perhaps the underlying fibrosis with septation and capsular hardening is a deterrent to rapid expansion and stretching of the capsule. The mechanism of hepatic failure has not been explained by massive necrosis or an alteration in hepatic circulation (3).

It is worthy of comment that the stigmata of cirrhosis and portal hypertension can occur (22) in both fatty metamorphosis and fatty cirrhosis, but that these have a much lower incidence than in advanced Laennec's cirrhosis (19, 20). Furthermore, they are more common in the fatty cirrhosis group than in the fatty metamorphosis group. However, esophageal varices may occur in patients with fatty metamorphosis alone, and may disappear with a fall in portal vein pressure in association with mobilization of fat (23).

Sudden death in patients with fatty livers has been mentioned previously in the literature. In 1944 Graham (24) reported five cases of young alcoholics aged 27 to 40 who died suddenly, and autopsy showed only a large fatty liver. Chemical analyses of the blood showed neither hypoglycemia nor very high alcohol levels. In 1951 Hartroft and Ridout (25) observed the entrance of lipid from fatty hepatic cysts into the biliary and vascular systems of experimental animals. Durlacher, Meier, Fisher, and Lovitt (26) in 1954 made fat stains of the lungs of 25 patients with alcoholic fatty livers who had died. In five cases massive pulmonary fat embolism was found, the quantity of fat in the pulmonary vessels being as great as or greater than that seen in traumatic fat emboli. Finally, Lynch, Raphael, and Dixon (27) in 1959 roughly attempted to quantitate the degree of fat embolization in various organs in 268 consecutive autopsy cases, 19 of which were alcoholics with fatty livers. In five cases pulmonary fat embolization was considered to be of such degree as to have played a major role in causing death. Although the presence of fat in the pulmonary vascular tree was not demonstrated in the present series due to the failure to do fat stains immediately after death, the clinical features of the nine patients who died suddenly (seven with fatty metamorphosis and two with fatty cirrhosis), plus the absence of any other known cause of death, are compatible with the occurrence of acute fat embolization.

There is nothing in the laboratory data that is specific for fatty metamorphosis. It has been said that there is no consistent difference in the laboratory patterns between fatty liver and portal cirrhosis (1, 18). Popper and Schaffner (8) found that in simple nutritional fatty liver the serum albumin was often decreased, the cephalin flocculation test was abnormal, and the alkaline phosphatase levels were increased in one-third of their cases; the most common laboratory abnormality was an increased bromsulfalein retention (1, 8). The data in the present series confirmed the frequency of bromsulfalein retention in fatty liver.

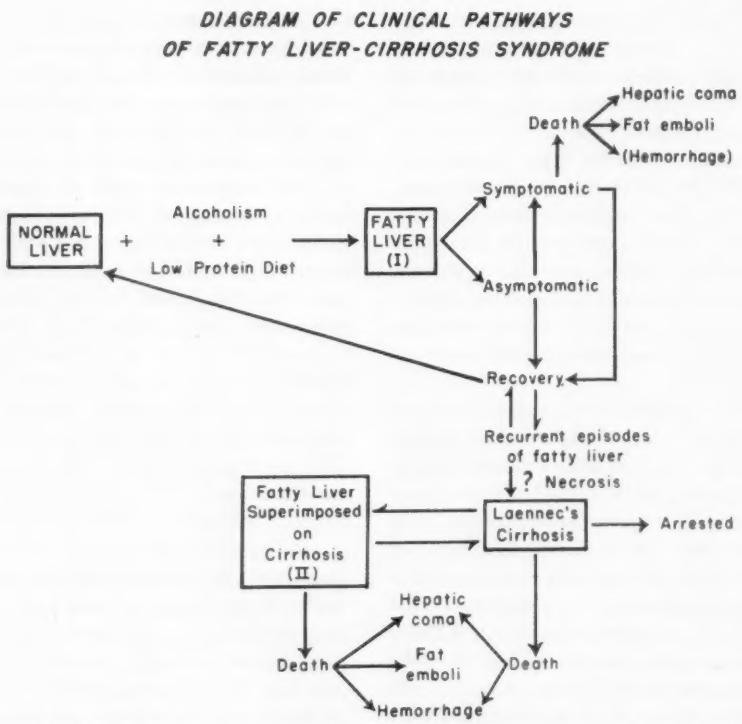


FIGURE 3. Diagram of the various possible clinical pathways in the fatty liver-cirrhosis syndrome based on the factors discussed in the text. Note that acute potentially reversible fatty metamorphosis may be superimposed upon a normal liver or upon a cirrhotic one.

There seems to be a difference between fatty metamorphosis and fatty cirrhosis with regard to serum protein alterations. All of the patients in Group I had a normal serum globulin, compared to 40% in Group II, and 65% of patients in Group I had a normal serum albumin, compared to 30% in Group II.

The syndrome of fatty liver, jaundice, hyperlipemia, and hemolytic anemia has been reported (28). Although 30% of the patients in Group I and 14% in Group II had an elevated serum cholesterol, significant anemia could not be correlated with hypercholesterolemia. Hyperglycemia and glycosuria have been noted in the course of acute fatty liver, and improvement in these abnormalities has occurred with improvement in the hepatic condition (1, 29). Four of our patients had an elevated blood sugar (none greater than 173 mg/100 ml), and in the two who survived, the hyperglycemia disappeared with improvement of hepatic function.

In patients with fatty livers who responded to therapy, serial liver biopsies have demonstrated evidence for mobilization of fat from the liver (1, 2, 16, 17). Seventy-six per cent of 63 cases of fatty liver showed decreased amounts of fat in one week (2). The intercellular fat was noted to disappear in three weeks, and fat within cysts was gone in six weeks (1). These facts emphasize the importance of early diagnosis and proper therapy. It is generally agreed that the essential aspects of a therapeutic regimen are rest and a high protein, high caloric diet (1, 16, 30,

31). Supplementary lipotropic agents and vitamins are not necessary if the patient is able to eat an adequate diet. No difference between high and low fat diets was found with respect to the rate of disappearance of fat from the liver. It is to be noted that there is a significant mortality associated with acute fatty metamorphosis and hepatic failure despite any type of therapy. Mortality may be as high as 20% (8).

The ultimate prognosis in patients with fatty livers who survive the initial episode is difficult to evaluate. In many of these patients, Laennec's cirrhosis eventually appears. This has been shown to occur by liver biopsies and autopsies in patients who continued to drink. Several patients who refrained from drinking and ate a nutritionally balanced diet showed no morphologic evidence of liver disease in subsequent biopsies (1, 2, 16, 17).

Figure 3 is a diagram of the various possible pathways occurring in the fatty liver-cirrhosis syndrome, based on some of the factors discussed in this paper. Acute fatty metamorphosis may occur in individuals with previously normal liver structure (Group I) or in cirrhotics (Group II). In both situations acute clinical manifestations may occur with jaundice, abdominal pain, and an increase in liver size, and death may result from hepatic failure, fat emboli, or hemorrhage. On the other hand, with proper therapy (adequate nutrition and abstention from alcohol), clinical improvement may occur in association with mobilization of the fat from the liver. In Group I recovery may result in the reappearance of normal histologic structure of the liver, and in Group II the irreversible cirrhotic changes remain. It is to be noted that recurrent episodes of acute fatty metamorphosis may occur in a single individual before and after the development of cirrhosis. Each of these episodes may be reversible or may result in death; the prognosis may be worse with increasing severity of the underlying cirrhosis.

Summary

The clinical and pathological data of 40 patients with histologically proven severe fatty metamorphosis of the liver have been analyzed. These patients were separated into two subgroups based on histologic changes in the liver: those with fatty metamorphosis (Group I) and those with fatty cirrhosis (Group II).

Alcoholism and malnutrition were predisposing factors in both subgroups. The mean age of the entire study group of 40 patients was younger than the mean age of several previously reported series of Laennec's cirrhosis. The patients with fatty metamorphosis were younger than those with fatty cirrhosis. The composition of the entire group with regard to race and sex indicated a relatively high proportion of Caucasians and females, especially in those patients who died.

Hepatomegaly was common in both subgroups, but spontaneous pain and hepatic tenderness were much more prominent findings in fatty metamorphosis. Clinical jaundice, present in one-half of all patients, was of greater intensity in fatty cirhosis. Ascites, edema, spider angiomata, splenomegaly, and esophageal varices were not common and, when present, occurred chiefly in patients with fatty cirrhosis.

Seven patients with fatty metamorphosis and two with fatty cirrhosis died suddenly with shock, dyspnea, or both, for which no cause could be found at autopsy. Evidence was cited to suggest that fat embolism may have been the cause of death in these patients.

The most consistent laboratory abnormality in both subgroups was bromsulfalein retention. Tests for hepatocellular function were more frequently abnormal in fatty cirrhosis. Hypoalbuminemia and hyperglobulinemia occurred in the majority of patients with fatty cirrhosis, whereas hypoalbuminemia was present in only 35% of patients with fatty metamorphosis and hyperglobulinemia was not observed. Hyper-

cholesterolemia or an increased serum level of alkaline phosphatase, or both, occurred with jaundice in both groups, even with minimal changes in other liver function tests, suggesting the presence of intrahepatic cholestasis.

Recurrent acute episodes of fatty metamorphosis may occur in alcoholics with either previously normal liver structure or with previous cirrhosis. In both situations acute clinical manifestations occur which may be reversible with proper therapy or may result in death due to hepatic failure, fat embolism, or hemorrhage.

Appendix—Illustrative Case Reports

case 1

This 36-year-old Negro male laborer was admitted on March 16, 1955. There was a history of ingestion of large amounts of whiskey since 1952. Three weeks prior to admission he began to experience epigastric pain, which occurred with meals and was unrelieved by antacids. The painful episodes were terminated by vomiting food he had just ingested. He had lost 19 pounds in the previous three months.

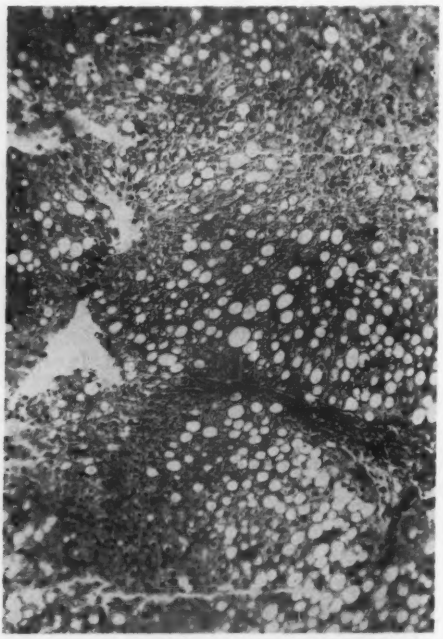


Figure 4. Liver biopsy in Case 1 showing 4+ fat and 1+ fibrosis (H & E; × 135).

Physical examination on admission revealed a temperature of 98 F, pulse 88/min, respirations 22/min, and blood pressure 140/100 mm Hg. No icterus was noted. The lungs were clear to auscultation and percussion. Cardiac examination was normal. The liver edge was palpated three fingerbreadths below the right costal margin in the mid-clavicular line. The edge was firm, rounded, nontender, and nonnodular. There was no splenomegaly, ascites, peripheral edema, spider angiomata, gynecomastia, testicular atrophy, or abnormal neurological sign.

The initial clinical impression was fatty metamorphosis of the liver, and the patient was placed on a high caloric, high carbohydrate, high protein diet. His appetite rapidly improved, and by March 26 he was considered ready for discharge.

A liver biopsy (Figure 4) was performed during the first week of his hospital stay, which showed 4+ fatty changes and 1+ fibrosis.

Laboratory studies showed a hemoglobin of 12.6 g/100 ml; white blood cell count, 7,200/mm^3; fasting blood sugar, 86 mg/100 ml; and blood urea nitrogen, 16 mg/100 ml. The urine was negative for bile and the urobilinogen value was not increased. Total serum proteins were 7.8 g/100 ml; albumin, 4.9 g/100 ml; and globulin, 2.9 g/100 ml. Total serum bilirubin was 0.6 mg/100 ml; prothrombin time, 98%; total serum cholesterol, 256 mg/100 ml with 71% esters. The cephalin-cholesterol flocculation was 1+ in 48 hr, thymol flocculation, 0, thymol turbidity, 2.2. The bromsulfalein test showed 39% retention in 30 min.

Comment: This case is an example of a patient manifesting abdominal pain and hepatomegaly without jaundice. Except for the bromsulfalein test his liver function studies were within normal limits. Note his good clinical response to dietary therapy plus abstinence from alcohol.

case 2

This 46-year-old white male unemployed laborer was admitted to the hospital on January 30, 1958, with the chief complaints of loss of appetite, abdominal pains, and yellow skin. For several years prior to admission he had drunk three to five shots of whiskey daily and one-fifth of a gallon on weekends. There was no known exposure to chemicals, insecticides,

drugs, injections, or transfusion. Two weeks before admission he began experiencing pain in the right upper quadrant associated with a sense of fullness and anorexia. He also noted yellow skin, dark brown urine, and greenish colored stools. For the previous two weeks he had experienced burning and "pins and needles" sensations on the soles of his feet.

On examination the temperature was 99.2 F, pulse 92/min, respiration, 20/min, blood pressure 110/80 mm Hg. He appeared to be well nourished and in no distress. His skin and sclerae were definitely icteric. He had palmar erythema and several spider angiomata on his anterior chest wall. His lungs were clear to auscultation and percussion, and cardiac examination was normal. The liver was markedly enlarged, smooth, firm, and moderately tender. The lower border was felt 14 cm below the right costal margin. The spleen was not palpable. There were no ascites and no peripheral edema. Neurological examination revealed impaired vibration sense at the ankles. The stool was clay-colored and negative for occult blood.

The initial impression was fatty cirrhosis. He was treated with bed rest and a 3,000 calorie, 450 g carbohydrate, 125 g protein diet supplemented by vitamins B-complex, C, and K.

Initial laboratory studies revealed hemoglobin, 11.1 g/100 ml; white blood cell count, 5,500/mm^3; blood sugar, 116 mg/100 ml; blood urea nitrogen, 7 mg/100 ml; the total proteins were 6.1 g/100 ml; albumin, 3.7 g/100 ml; and globulin, 2.4 g/100 ml; prothrombin time was 44%; total cholesterol, 473 mg/100 ml, with 39% esters; alkaline phosphatase, 10.2 Bodansky units; total bilirubin, 6.6 mg/100 ml, with 3.3 mg/100 ml "one-minute" bilirubin; the thymol turbidity was 2.2 units; and the cephalin-cholesterol and thymol flocculation tests were negative; the level of serum glutamic oxaloacetic transaminase was 184 units; and the 24-hr urine urobilinogen level was 24.8 Ehrlich units.

Shortly after admission, his appetite improved and his clinical jaundice progressively decreased. By the fourteenth hospital day his stools were dark brown. On the eighteenth hospital day his total bilirubin was 2.7 mg/100 ml, with the "one-minute" bilirubin showing 1.1 mg/100 ml; total proteins were 6.2 g/100 ml, alkaline phosphatase, 3.7 Bodansky units, total cholesterol, 277 mg/100 ml, with 53% esters; prothrombin time was 73%. On the twenty-first hospital day his bromsulfalein test showed 29% retention in 30 min, and his liver had decreased in size to 6 cm below the right costal margin.

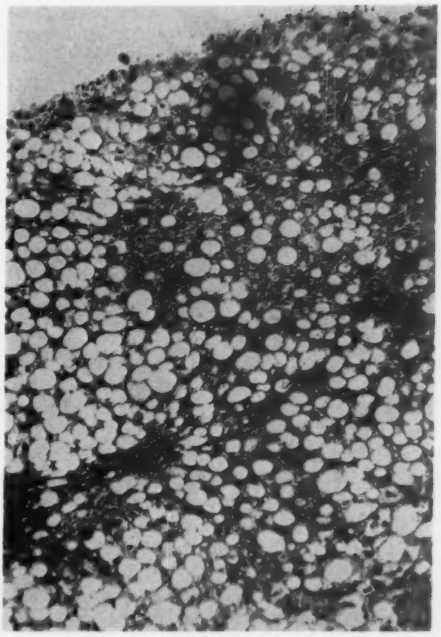


FIGURE 5. Liver biopsy in Case 2 showing 4+ fat and 2+ fibrosis (H & E; × 135).

A needle biopsy of the liver showed 4+ fat and 2+ fibrosis at the end of his first week of hospitalization (Figure 5). An upper gastrointestinal series and a barium enema X-ray examination were negative. A cholecystogram using a double dose of dye revealed a nonfunctioning gall bladder.

Comment: This patient illustrates the problem of abdominal pain, jaundice, hepatic tenderness, and the laboratory picture compatible with obstructive jaundice in a patient with fatty metamorphosis of the liver. The flocculation tests and albumin-globulin ratio were normal, with elevated serum cholesterol and alkaline phosphatase levels. The level of serum glutamic oxaloacetic transaminase was in the range seen in obstructive jaundice. The problem was resolved by clinical observation and needle biopsy.

CASE 3

This 45-year-old white male had a history of ingestion of one quart of whiskey daily for

several years. He had three admissions to Philadelphia General Hospital. He was first admitted in May, 1942, because of jaundice. Physical examination revealed a confused white male manifesting auditory and visual hallucinations, with icterus of the skin and sclerae and a slightly tender liver edge two and one-half fingerbreadths below the right costal margin. He was treated with fluids, paraldehyde, and large dosages of vitamins B-complex and C. Gradual clinical and laboratory improvement was noted and he was discharged three weeks after admission. The icterus index was 144 units initially and gradually fell to 48 units. Total serum cholesterol was 346 mg/100 ml, with 7% esters; urine was positive for bile.

He was re-admitted in November 1942 with jaundice and delirium tremens. His liver was four fingerbreadths below the right costal margin and was firm and hard. Pitting edema of the ankles was noted. He was treated with fluids, high caloric diet, vitamins, and sedation. By his twentieth hospital day his mental picture had cleared, and by his thirty-second hospital day the liver was scarcely palpable.

Laboratory studies revealed an initial icterus index of 152 units which decreased to 74 units; total proteins, 4.9 g/100 ml; total cholesterol, 160 mg/100 ml, with 5% esters; prothrombin time, 53%; the urine was positive for bile. He was discharged one month after admission.

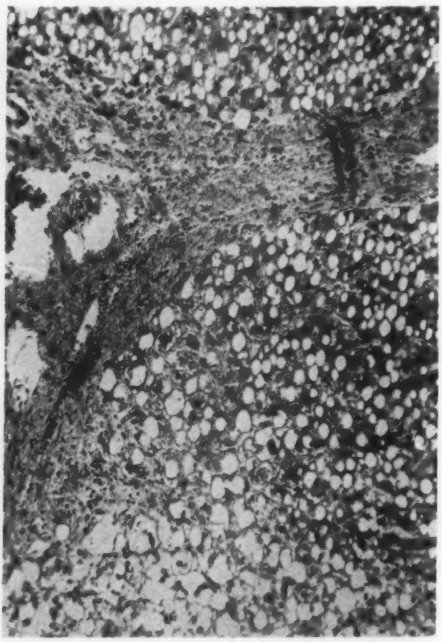


FIGURE 6. Liver at autopsy in Case 3 showing 4+ fat and 3+ fibrosis (H & E; × 135).

The final admission was in February, 1946, at which time he manifested jaundice of two weeks' duration with dark urine and light stools. No pain, nausea, or vomiting was experienced.

The temperature was 99 F, pulse, 80/min, respirations, 26/min, blood pressure, 130/78 mm Hg. There was marked jaundice of the skin and sclerae. No spider angiomata were noted. The liver was markedly enlarged, with the right lobe reaching to the level of the umbilicus. The spleen was not palpable. The rest of the examination was normal. The impression at this time was Laennec's cirrhosis with intrahepatic obstruction.

Shortly after admission, he developed a generalized convulsive seizure followed by coma, and died on the fourth hospital day. Therapy consisted of intravenous glucose and water, vitamins, and penicillin.

Laboratory studies on this admission included hemoglobin, 11.5 g/100 ml; white blood cell count, 9,400/mm^3; icterus index, 152 units; total serum proteins, 6.4 g/100 ml; albumin, 3.4 g/100 ml; globulin, 3 g/100 ml; total cholesterol, 174 mg/100 ml, with 21% esters; and the cephalin-cholesterol flocculation test was 3+.

Significant autopsy findings were obesity, marked jaundice, acute congestion and edema of the lungs, slightly enlarged spleen, and markedly enlarged, fatty, greenish-yellow liver. On microscopic examination the liver showed 4+ fat and 3+ fibrosis (Figure 6). The rest of the autopsy revealed no other significant abnormalities.

Comment: This case illustrates recurrent episodes of hepatic failure in an alcoholic over a period of five years, of which the first two episodes responded to therapy and the final episode ended in death in hepatic coma. At autopsy the patient had severe fatty changes of the liver with an underlying cirrhosis, and it is reasonable to assume that the previous episodes were associated with acute hepatic steatosis which was reversible to some degree.

CASE 4

This 43-year-old white male shipper was admitted to the hospital on July 21, 1950, with

jaundice and hallucinations. For several years prior to admission he had ingested approximately two gallons of wine per week. For about one year before admission his food intake had decreased markedly due to progressive anorexia. A few days before coming to the hospital he noted a yellow color to his skin and eyes, an increase in the size of his abdomen, and a dark color to his urine. At this time he became acutely psychotic.

On admission he manifested paranoid tendencies, delusions, and visual and auditory hallucinations. His vital signs were normal. He was obese and had definite icterus. His tongue was beefy red, and cheilosis was present. Gynecomastia and several spider angiomata were noted. The lungs were clear to auscultation and percussion, and the heart was normal. The right lobe of the liver was enlarged, the lower border extending below the level of the umbilicus. It was firm, non-nodular and nontender. The left lobe was also markedly enlarged. There was no splenomegaly, ascites, or edema. Neurological examination was normal. The initial impression was Laennec's cirrhosis.

Initial laboratory data included hemoglobin, 12.9 g/100 ml; fasting blood sugar, 67 mg/100 ml; blood urea nitrogen, 12 mg/100 ml; total serum proteins, 9.2 g/100 ml; total serum cholesterol, 347 mg/100 ml, with 46% esters; prothrombin time, 23%; cephalin-cholesterol flocculation 4+ in 48 hours; thymol flocculation 4+; and thymol turbidity 13 units.

Therapy consisted of rest, high protein, high carbohydrate, low fat diet, choline chloride, brewers' yeast tablets, crude liver extract, ascorbic acid, and vitamin K. By the twenty-fourth hospital day, the clinical jaundice was moderately improved and his sensorium had cleared.

Shortly prior to discharge his laboratory studies showed total proteins, 9.1 g/100 ml; albumin, 4 g/100 ml; globulin, 5.1 g/100 ml; total bilirubin, 4.63 mg/100 ml; alkaline phosphatase, 2.47 Bodansky units; prothrombin, 28%; and bromsulfalein retention 32% in 30 min. A liver biopsy performed five days after hospital admission showed 3+ fat and 4+ fibrosis (Figure 7).

Comment: This case illustrates the clinical complex of alcoholism, jaundice, hepatomegaly, and psychopathy without obvious pain or tenderness in a patient with advanced cirrhosis and superimposed fatty metamorphosis. Improvement was slow.

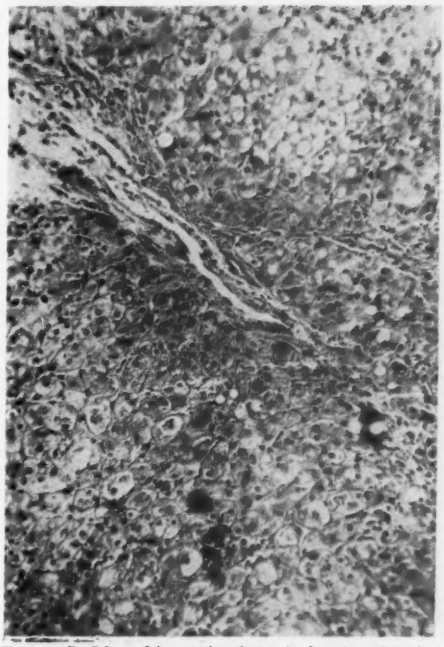


FIGURE 7. Liver biopsy in Case 4 showing 3+ fat and 4+ fibrosis (Trichrome; × 135).

CASE 5

This middle-aged white male, a chronic alcoholic, was brought to the hospital because of convulsions of recent onset. When first seen in the receiving ward he was cyanotic and severely dyspneic. He was given 500 mg of caffeine sodium benzoate intravenously, following which he appeared to be more comfortable. Upon arrival on the ward his pulse was weak, rapid, and thready; blood pressure was 90/58 mm Hg. No jaundice was noted. The liver edge was 2 inches below the right costal margin; the spleen was not palpable. There was no peripheral edema. Neurological examination showed no focal abnormalities. Initial impressions were cirrhosis of the liver with bleeding varices or acute cardiac failure with pulmonary edema. He was given 90 cc of 50% glucose intravenously, together with 500 mg of caffeine sodium benzoate. Very shortly afterwards he died. The time between admission and death was probably not more than 60 min.

Positive findings at autopsy were: severe congestion of the lungs, which microscopically showed marked edema and some patchy areas of atelectasis and minimal pneumonitis; moderately enlarged yellow fatty liver which micro-

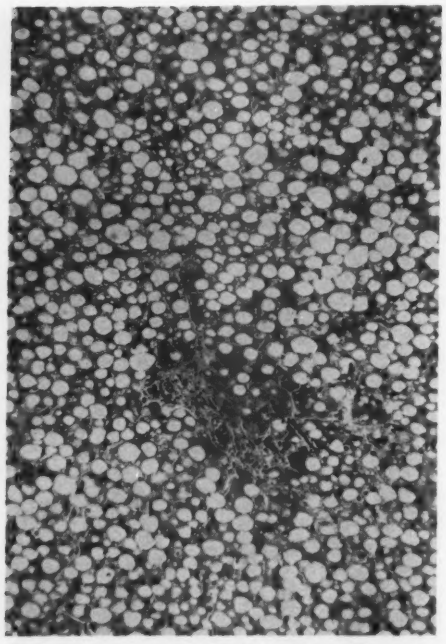


FIGURE 8. Liver at autopsy in Case 5 showing 4+ fat and 1+ fibrosis (H & E; × 135).

scopically showed 4+ fat (extreme fatty metamorphosis) and 0 to 1+ fibrosis (Figure 8). There was no evidence of myocardial disease or gastrointestinal bleeding. No other significant gross or microscopic abnormalities were noted.

Comment: This case is a typical example of an alcoholic patient with severe fatty metamorphosis of the liver dying in acute respiratory distress and shock for which no known cause could be found.

CASE 6

This 32-year-old white male had been a chronic alcoholic for several years prior to admission. He was admitted to the hospital in September, 1950, complaining of a lump in his abdomen, abdominal pain, and vomiting. For one and one-half years prior to this admission he had had recurrent episodes of the above symptoms. He was admitted to another hospital in 1948 and treated by gastric intubation and intravenous fluids with symptomatic response. Subsequently he suffered intermittent mild attacks of right upper quadrant pain and vomiting.

In 1949 he was admitted to a second hospital for a right upper quadrant mass, but refused surgery and signed out of the hospital in two weeks without a diagnosis. One week before the present admission he developed paroxysms of vomiting associated with drinking large amounts of wine.

On admission his vital signs were normal. The blood pressure was 154/100 mm Hg. The skin was cold and sweaty. No icterus was noted. The heart and lungs were normal. His abdomen was distended, and a slightly tender mass was palpated in the right upper quadrant two fingerbreadths below the right costal margin. Neurological examination revealed hyperactive deep tendon reflexes with no pathological reflexes.

The differential diagnoses of the mass included hepatomegaly, an enlarged gall bladder, or a pancreatic cyst.

Laboratory studies revealed: hemoglobin, 14.4 g/100 ml; white blood cell count, 7,000/mm^3; blood sugar, 83 mg/100 ml; blood urea nitrogen, 12 mg/100 ml. The serum amylase was 37 mg/100 ml; bromsulfalein retention, 12% in 30 min; the cephalin-cholesterol, thymol flocculation, and thymol turbidity tests were nega-

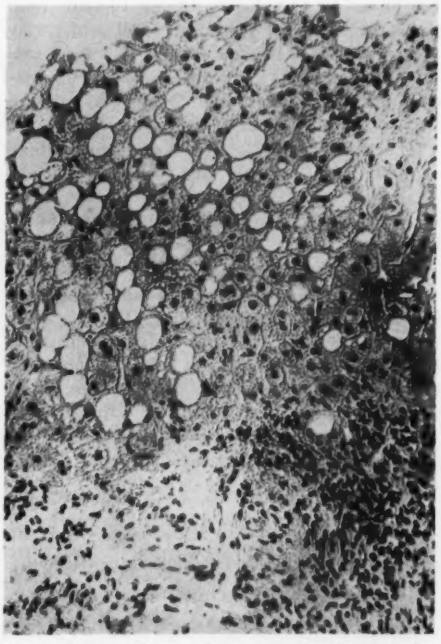


FIGURE 9. Liver biopsy in Case 6 showing 3+ fat and 1+ fibrosis (H & E; × 175).

tive; total serum proteins were 7.7 g/100 ml; albumin, 5.9 g/100 ml; globulin, 1.8 g/100 ml; prothrombin, 45%; total bilirubin, 6.16 mg/100 ml; total cholesterol, 380 mg/100 ml, with 81% esters; and 24-hr urine urobilinogen, 5.4 Ehrlich units. X-ray examinations of the gall bladder, the urinary tract, and the entire gastrointestinal tract were negative.

A liver biopsy was done shortly after admission (Figure 9) and showed 4+ fat and 1+ fibrosis. On dietary therapy and rest, the patient improved symptomatically, the "mass" regressed, and he was discharged in November 1950.

Comment: This case illustrates the problem of a patient with fatty liver presenting with abdominal pain and an "undiagnosed" abdominal mass. The mass subsequently proved to be an unusually-shaped right lobe of the liver. Most liver function studies were normal in the presence of marked fatty changes in the liver. Exceptions were the slightly abnormal bromsulfalein test and prothrombin time.

Summario in Interlingua

Es analysate le datos clinic e pathologic de 40 patientes con histologicamente demonstrate sever metamorphose grassiose del hepate. Le patientes esseva dividite in duo subgruppos a base del alterationes histologic in le hepate. Gruppo I consisteva de casos de metamorphose grassiose e gruppo II de casos de cirrhosis grassiose.

Alcoholismo e malnutrition esseva factores predisponitori in ambe subgruppos. Le estate medie pro le gruppo total de 40 patientes esseva plus basse que le etates medie in plure previemente reportate series de cirrhosis de Laennec. Le patientes con metamorphose grassiose esseva plus juvene que illes con cirrhosis grassiose. Le composition del gruppo total con respecto a racia e sexo indicava un relativemente alte proportion de caucasianos e de femininas, specialmente inter le patientes qui moriva.

Hepatomegalia esseva commun in ambe subgruppos, sed spontanee dolores e hyperesthesia hepatic esseva multo plus prominente in metamorphose grassiose. Jalnessa clinic, presente in un medietate de omne le patientes, esseva plus intense in cirrhosis grassiose. Ascites, edema, nevos arachnoidee, splenomegalia, e varices esophagee non esseva commun. In tanto que illos occurreva, illos se trovava principalmente in casos con cirrhosis grassiose.

Septe patientes con metamorphose grassiose e duo con cirrhosis grassiose moriva subitemente con choc e/o dyspnea. Pro isto nulle causa esseva trovabile al necropsia. Es signalate datos que indica que embolismo grassiose esseva possibilemente le causa del morte de iste patientes.

Le plus constante anormalitate laboratorial in ambe subgruppos esseva retention de bromsulfaleina. Tests del function hepatocellular esseva plus frequentemente anormal in cirrhosis grassiose. Hypoalbuminemia e hyperglobulinemia occurreva in le majoritate del patientes con cirrhosis grassiose, durante que hypoalbuminemia esseva presente in solmente 35% del patientes con metamorphose grassiose, e hyperglobulinemai non esseva observate in iste gruppo del toto. Hypercholesterolemia e/o augmentate nivellos seral de phosphatase alcalin occurreva con jalnessa in ambe gruppos, mesmo si le alterationes indicate per altere tests del function hepatic esseva minime. Isto suggereva le presentia de cholestasis intrahepatic.

Recurrente episodios acute de metamorphose grassiose pote occurrer in alcoholicos tanto con previemente normal structuras hepatic como etiam con antecedente de cirrhosis. In ambe situationes acute manifestationes clinic occurre que pote esser reversibile sub le effecto de un appropriate therapia o que pote resultar in le morte del patiente in consequentia de disfallimento hepatic, de embolismo de grassia, o de hemorrhagia.

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Observations on Secondary Malabsorption Syndromes of Intestinal Origin

Regional Enteritis, Lymphoma, Jejunal Diverticulosis, Gastrojejunocolic Fistula

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MALABSORPTION SYNDROMES may occur in any of the diseases or conditions which impair absorption from the small intestine. It may be impaired by faulty digestion within the small intestine, by conditions that interfere directly with the process of absorption, or by abnormalities of the stomach.

A classification based on the site and mechanism of the malabsorptive defect is given in Table 1 (1, 2). The origin of the defect may be from the small intestine or its mesentery, from gastric abnormalities, from pancreatic disease leading to a pancreatic enzyme insufficiency, or from hepatobiliary conditions causing a lack of bile salts. The noninsulin producing islet-cell tumors may cause a malabsorption syndrome by stimulating increased secretion of gastric acid which interferes with the action of pancreatic enzymes (3, 4). The malabsorption syndromes of intestinal origin may be primary, when the defect is mainly within the mucosa as in nontropical sprue, or secondary, when some additional disease or condition exists.

In this report on secondary malabsorption syndromes of intestinal origin special consideration will be given to those associated with regional enteritis, lymphoma, jejunal diverticulosis, and gastrojejunocolic fistula. Several general references dealing with malabsorption syndromes will be cited, but an exhaustive review of the literature has not been attempted (1, 2, 4–7).

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PATHOPHYSIOLOGY

Malabsorption syndromes, in general, are characterized by diarrhea, loss of weight, weakness, steatorrhea, anemia, and various evidences of nutritional deficiency resulting from defective digestion and absorption of the various nutrients (fat, carbohydrate, and protein), vitamins (A, B-complex, B_{12}, folic acid, C, D, and K), minerals (iron, calcium, phosphorus, potassium, sodium, and chlorides), and even water. Steatorrhea is probably the com-

TABLE 1. Classification of the Malabsorption Syndromes Based on the Site of Origin and Mechanism of Development

Intestinal: Defect of small intestine or mesentery.	
A. Primary: nontropical sprue, tropical sprue, and celiac disease.	
B. Secondary: specific cause recognized.	
Gastric: Inadequate mixing of food, enzymes, and bile salts; lack of intrinsic factor.	
Postgastrectomy state (total, subtotal).	
Pernicious anemia.	
Pancreatic: Lack of enzymes, especially lipase.	
Chronic pancreatitis and calculi.	
Atrophy, carcinoma, and fistulas.	
Postpancreatectomy state.	
Fibrocystic disease.	
Noninsulin producing islet-cell tumor.	
Hepatobiliary: Lack of bile salts.	
Obstructive jaundice and biliary cirrhosis.	
Hepatitis and cirrhosis.	

TABLE 2. Secondary Malabsorption Syndromes of Intestinal Origin

1. Regional enteritis (5, 9–11).
2. Amyloidosis (12, 13).
3. Scleroderma [systemic sclerosis] (14–16).
4. Radiation [actinic] enteritis (2, 5, 17, 18).
5. Whipple's disease (7, 19–23).
6. Lymphoma (24, 25), carcinoma, carcinoid (26).
7. Tuberculosis [tabes mesenterica] (2).
8. Surgical resections, short circuits (6, 27).
9. Diverticula (4, 28, 29), blind loops (30), strictures (6).
10. Internal fistulas [gastrojejunocolic] (31).
11. Parasites [Giardia, Diphyllobothrium] (32).
12. Acute enteritis [viral, bacterial] (33).
13. Diabetes mellitus with neuropathy (2).
14. Mesenteric vascular insufficiency (34).
15. Intestinal abnormalities (35).
16. Drug induced [neomycin (36), phenindione (37)].

monest and most significant of the defects, but other defects, either alone or in combination, may be present without impaired absorption of fat. In addition, nontropical sprue and some of the secondary intestinal malabsorption syndromes may be complicated by loss of albumin and perhaps other substances into the digestive tract (8).

Some of the mechanisms which may lead to impaired or incomplete digestion and absorption from the small intestine are: (1) inadequate intake; (2) insufficient hematopoietic intrinsic factor; (3) inadequate digestive enzymes and bile; (4) improper mixing of food, enzymes, and bile; (5) biochemical or enzymatic dysfunction of the mucosal cells; (6) intrinsic disease of the intestinal wall; (7) inadequate length of normal intestinal surface; (8) altered intraluminal pressure or motility; (9) obstruction of the mesenteric lymph or blood vessels; (10) alterations of the autonomic nervous system; and (11) bacterial or parasitic interference with absorption. One or a combination of these factors is concerned in any disease of the small intestine or its mesentery that produces a specific malabsorption syndrome.

CLASSIFICATION

Most of the common causes of secondary malabsorption syndromes of intestinal origin are listed in Table 2 with references to some of the recent contributions (1, 2). Some of these conditions will not be considered any further; others will be mentioned briefly at this point or discussed in detail later in this report.

Amyloidosis: Amyloidosis of the small intestine may produce a malabsorption syndrome (12). Steatorrhea with excretion of 15 and 27 grams of fat in the feces per day, respectively, was noted by Green, Higgins, Brown, Hoffman, and Somerville (13) in two cases of amyloidosis involving the small intestine. Peroral intubation biopsy of the small intestine established the diagnosis of amyloidosis in five of six patients with proved amyloidosis. Amyloid was present in the walls of arteries, basement membranes, and muscularis mucosae.

Scleroderma (Systemic Sclerosis): Steatorrhea or other evidence of malabsorption may be seen in patients with scleroderma of the small intestine (14–16). Eleven of 18 such patients seen at the Mayo Clinic were tested for steatorrhea; chemical evidence of it was found in six, and microscopic evidence in three others. The steatorrhea was usually less disturbing to the patient than the anorexia, dysphagia, vomiting, and constipation. Changes seen on roentgenologic examination of the small intestine that may be factors contributing to the steatorrhea are dilatation, slowed motility, or a deficiency pattern. Pathologic changes of significance include atrophy of the muscularis, edema with hyperemia of the submucosa, and atrophy of the mucosa with disorganization of villi and infiltration with lymphocytes (14). In one of our patients that came to post-mortem examination, the upper two-thirds of the small intestine was involved, but not the lower third.

Radiation (Actinic) Enteritis: Three cases of malabsorption syndrome secondary to actinic enteritis have been reported from this clinic previously (2, 17). Reeves, Sanders, Isley, Sharpe, and Baylin (18)

found that steatorrhea developed in 13 of 29 patients with tumors of the cervix who were treated with radiation over the abdomen. A malabsorption syndrome, intermittent, partial obstruction of the small intestine, and hypochromic anemia due to chronic loss of blood are the main conditions that may develop two to 20 years after radiation therapy of the lower part of the abdomen for malignant lesions (17). The response depends on the dosage given and the individual tissue sensitivity. Factors that may lead to malabsorption include partial obstruction with proximal dilatation and altered motility and changes in the bowel wall including fibrous replacement of the muscularis and thickening of blood vessels in the submucosa. Resection of the involved segment of bowel usually is a part of the therapeutic program.

Whipple's Disease: Experience with six patients ill with Whipple's disease at the Mayo Clinic has been reported previously (19). Two of these patients have subsequently demonstrated good remissions during the administration of adrenocortical steroids. Other internists have emphasized the importance of steroids (23), nitrogen mustard (20), or antibiotics (21) in the treatment of Whipple's disease. The diagnosis is based in part on the demonstration of macrophagocytosis in the tunica propria of the small bowel and of lipogranulomatosis in the mesenteric lymph nodes obtained at laparotomy. The granules in the macrophages stain well with periodic acid-Schiff stain but poorly with Sudan. Diagnosis has been established from biopsy of peripheral lymph nodes and peroral biopsy of the small intestine (21, 23).

Recent studies (22) with the aid of light and electron microscopes and special techniques have demonstrated abundant large, sickle-form particle-containing cells in the lamina propria of the small intestine and in the mesenteric lymph nodes as well as in the tissues of all major organ systems. This suggests that Whipple's disease is a systemic affliction rather than just an intestinal lipodystrophy. These findings and future studies may lend further insight into the etiology and may explain the wide variety of signs and symptoms in addition to those usually seen in a malabsorption syndrome.

Regional Enteritis

Steatorrhea or other evidence of malabsorption is frequently observed in regional enteritis (9, 10). Ensrud and Sauer (9) found evidence of malabsorption in ten of 38 patients (26%) who had never undergone operation on the small intestine. The mechanisms concerned with the production of one or more of the malabsorptive phenomena include disease of the intestinal wall, the extent of the small intestine involved, formation of internal fistulas or short circuits with bacterial contamination, and development of strictures with partial obstruction, stagnation, and altered bacterial flora. The presence of abdominal pain, fever, tender abdominal mass, fistulas, and other evidence of chronic infection will help distinguish regional enteritis from nontropical sprue. Often this differentiation is difficult to make, and a patient may be given one of these diagnoses and only later will it be discovered that the other condition actually existed. Roentgenographic examination of the small intestine usually shows pronounced narrowing of the lumen over a long segment with interposed zones of dilated intestine, loss of normal mucosal markings, internal fistulas, or even a deficiency pattern as in nontropical sprue.

CASE 1

A 41-year-old white married woman, the mother of eight children, was admitted June 19, 1958, with complaints of intermittent diarrhea for 20 years and inability to maintain her weight. The diarrhea varied in severity from three to ten bowel movements in 24 hours.



FIGURE 1 (*case 1*). Regional enteritis with malabsorption syndrome. Narrowing of the lumen of the ileum and the dilated zones should be noted. (Reproduced by permission of *Mississippi V. Med. J.* 81: 162, 1959).

Stools were described as liquid, frothy, and foul-smelling. She had noted some right lower quadrant abdominal cramps and abdominal distention at the end of the day that would disappear by morning. Urination twice a night had been present for two years. Her maximal weight had been 105 pounds. An operation for a fistula in ano had been performed in 1944.

Physical examination disclosed a chronically ill-appearing woman weighing only 88 pounds. A 4 cm mass was palpated in the right lower quadrant of the abdomen and increased pigmentation was noted in the skin on the back and legs.

Laboratory studies revealed the following values: erythrocytes, 4,520,000, leukocytes 4,000/mm^3 of blood; hemoglobin, 12.4 g/100 ml, and sedimentation rate 87 mm in 1 hour by the Westergren method. The blood smear showed moderate rouleaux formation and 76% neutrophils. The value for serum carotene was 44 international units/100 ml; for calcium, 8 mg/100 ml, and for phosphate, 5.2 mg. The alkaline phosphatase was 9 King-Armstrong units. The total serum proteins measured 4.65 g/100 ml with an albumin-globulin ratio of 2.50 : 2.15. The prothrombin time was 18 seconds. Quantitative chemical analysis of stool specimens collected over a 72-hour period while the patient was taking 102 g of fat a day revealed the following values: total fat, 46 g or 24% of the total solids, and total nitrogen, 13.8 g. This amounted to 15.3 g of fat excreted per day and 4.6 g of nitrogen. Excretion of more than 7.5 g of fat is considered to represent steatorrhea, and 2.5 g of nitrogen, azotorrhea. Proctoscopic examination revealed external hemorrhoids and an anal stricture. Roentgenograms of the thorax and colon were negative. Roentgenologic examination of the small bowel after a barium meal showed regional enteritis involving most of the lower part of the ileum, but the jejunum and upper

part of the ileum seemed to be normal (Figure 1).

The patient was treated with a nutritious, low-residue diet containing 80 g of fat, 1 g of salicylazosulfapyrine (Azulfidine) four times a day on alternate weeks, a multivitamin capsule daily, 50,000 units of vitamin D (Drisdol) and 4 mg of vitamin K analog (Synkamin) twice a week. The initial improvement was good, but long-term follow-up has not been obtained.

Comment: In this case regional enteritis with associated malabsorption syndrome was characterized by loss of weight, steatorrhea, azotorrhea, hypocarotenemia, and hypocalcemia. A gluten-free diet is seldom helpful in patients with regional enteritis. Steroids may be required temporarily in severe cases (10, 11). Surgical treatment may be necessary in the presence of fistulas, strictures, or other complications.

MALABSORPTIVE DEFECTS IN EIGHT PATIENTS

The main symptoms and physical and laboratory findings in eight nonsurgical patients having regional enteritis and a malabsorption syndrome, including Case 1, are shown in Table 3. Diarrhea, loss of weight, and an abdominal mass were present in all or nearly all patients, and abdominal tenderness was present in three of them. Steatorrhea, hypocalcemia, and hypoalbuminemia were the commonest signs of malabsorption. Hypokalemia, hypocarotenemia, and azotorrhea or excess fecal loss of nitrogen were commonly observed. Hypochromic anemia, usually of mild degree, was present in five patients. None showed macrocytic anemia, although this may occur. An elevated sedimenation rate was noted in six patients.

LYMPHOMA

Sometimes lymphomas may produce a malabsorption syndrome by extensive involvement of the small bowel with or without partial intestinal obstruction, formation of fistulas, or blockage of the lymphatic system in the mesentery (24, 25).

TABLE 3. Malabsorptive Defects in Eight Nonsurgical Cases of Regional Enteritis and a Malabsorption Syndrome

Finding or Defect	Cases*
Diarrhea	8 (8)
Loss of weight (avg 29 pounds)	8 (8)
Abdominal pain	6 (8)
Abdominal mass	5 (8)
Steatorrhea (> 7.5 g per day) Fecal fat (8–46, avg 17 g per day) (13–43, avg 28% of solids)	8 (8)
Azotorrhea (> 2.5 g per day) Fecal nitrogen (3.8–6.2, avg 4.8 g per day)	4 (7)
Hypocarotenemia (< 40 IU per 100 ml)	4 (5)
Hypocalcemia (< 9.2 mg per 100 ml)	8 (8)
Hypoprothrombinemia (prothrombin time > 20 seconds)	3 (8)
Hypoalbuminemia (< 3.5 g per 100 ml)	7 (8)
Hypokalemia (< 4.0 mEq per liter)	3 (4)
Hypochromic anemia (< 12 g per 100 ml)	5 (8)
Oral glucose tolerance test (flat curve)	3 (5)
Erythrocyte sedimentation rate (> 30 mm in 1 hour)	6 (8)

* Numbers in parentheses indicate number of patients in the group examined or undergoing tests for the condition.



FIGURE 2 (*case 2*). Lymphoma with malabsorption syndrome. The deformity of the duodenum and dilatation of the stomach and upper part of small bowel should be noted.

The incidence of this syndrome in patients with abdominal lymphoma is relatively low. Often other symptoms are more prominent so that the existence of minor degrees of malabsorption are overlooked. The clinical features resemble nontropical sprue, but the onset and course may be more abrupt in patients with lymphoma. The presence of an abdominal mass, fever, abdominal cramps, or bleeding may aid in diagnosis. Anemia is common and is more often hypochromic than macrocytic. Roentgenographic examination of the small intestine may show a deficiency pattern, multiple small nodular defects, infiltration of the intestinal wall, or constriction of the lumen with dilatation above it. Abdominal exploration or biopsy of peripheral lymph nodes is necessary to establish the diagnosis. Peroral biopsy of the small intestine in three patients revealed suggestive, but not diagnostic, changes. The following pathologic types of lymphoma have been represented: reticulum cell sarcoma, giant follicle, small cell lymphoblastoma, and Hodgkin's sarcoma. Roentgen or nitrogen mustard therapy in addition to nutritional supportive measures is indicated in treatment. The prognosis is poor, as most patients die within three years after onset of symptoms.

CASE 2

A 34-year-old married white woman was admitted April 30, 1956, because of diarrhea, epigastric pain, vomiting, fatigue, and loss of weight. Since the age of seven, she had suffered most of the time from diarrhea, consisting at admission of six to eight large, frothy, liquid stools a day. At age 27, tetany developed, and she had taken supplemental calcium since. For the past two years she had noted epigastric pain, somewhat relieved by vomiting, with bloating, melena, and hematemesis, and she had received 33 pints of blood by intravenous infusion. She had lost 40 pounds and had noted increased fatigue. A large, cystic tumor, apparently of the left ovary, had been removed in 1950.

Physical examination revealed a malnourished woman weighing only 94 pounds. There were mild diffuse melanosis, slight clubbing of the fingers, and positive Trousseau's and Chvostek's signs. The lower part of the abdomen was somewhat distended with visible peristaltic action and borborygmus with increased frequency and pitch of bowel sounds.

Laboratory studies yielded the following values: erythrocytes, 2,900,000, leukocytes, 4,100/mm³ of blood; hemoglobin, 7.8 g/100 ml; sedimentation rate 38 mm in 1 hour by the Westergren method. The blood smear suggested hypochromic anemia. The value for serum calcium was 8.3 mg/100 ml; for phosphate, 2.3 mg; for potassium 3.7 mEq/liter, and for total proteins, 5.1 g/100 ml with an albumin-globulin ratio of 2.98 : 2.12. The value for fasting blood sugar was 100 mg/100 ml, and the prothrombin time, 22 seconds (normal 16 to 19) which was reduced to 18 seconds after the administration of vitamin K. Stool collections were performed on two occasions while the patient was taking a general diet the first time and an ulcer diet the second time. The fecal

excretion of fat amounted to 31 g per day (58% of total solids) and 47.4 g per day (77% of total solids), respectively. The values for fecal nitrogen were 2.3 and 2.4 g per day. On roentgenologic examination following a barium meal, the stomach and proximal portion of the small bowel were found to be dilated and filled with fluid as though secondary to an obstructive process, and a moderate deformity of the duodenal cap suggested duodenal ulcer (Figure 2). The tremendously dilated, redundant, atonic colon suggested a secondary megacolon.

It was thought that this patient had some sort of malabsorption syndrome with an additional obstructing duodenal ulcer and that surgical intervention was advisable. At operation the colon was markedly dilated without evidence of obstruction. At the mid-portion of the jejunum, there was an annular tumor, and proximal to this there were at least three other smaller tumors. A similar area in the duodenum probably had caused the deformity seen on the roentgenogram. Specimens of the tumors and lymph nodes were taken, and a posterior gastrojejunostomy was performed. The pathologist reported lymphoblastoma of Hodgkin's type and an inflammatory node. The patient's symptoms persisted despite general supportive measures until she died on November 3, 1956.

Comment: This patient had a malabsorption syndrome secondary to lymphoma of the duodenum and jejunum manifested by steatorrhea, loss of weight, hypochromic anemia, hypocalcemia, and hypoprothrombinemia. It is possible that she had suffered from celiac disease or nontropical sprue since childhood and that the lymphoma was superimposed with aggravation of symptoms. Unfortunately her condition was too poor to justify intestinal biopsies and post-mortem examination was not done.

MALABSORPTIVE DEFECTS IN NINE PATIENTS

Some of the significant findings and malabsorptive defects in nine cases of lymphoma and malabsorption syndrome including Case 2 are given in Table 4. Diarrhea, loss of weight, weakness, and abdominal distress were important symptoms, and abdominal distention, lymphadenopathy, and abdominal mass were helpful findings. The malabsorptive defects were diversified and rather uniformly present in the patients. All seven patients

TABLE 4. Main Findings and Malabsorptive Defects in Nine Cases of Lymphoma and Malabsorption Syndrome

Finding or Defect	Cases*
Diarrhea	9 (9)
Loss of weight	8 (9)
Abdominal distress	8 (9)
Abdominal distention	4 (9)
Steatorrhea (> 7.5 g per day) Fecal fat (9–56, avg 38 g per day) (28–67, avg 47% of solids)	9 (9)
Azotorrhea (> 2.5 g per day) Fecal nitrogen (3.1–5.1, avg 4.1 g per day)	4 (5)
Hypocalcemia (< 9.2 mg per 100 ml)	6 (7)
Flat oral glucose tolerance test	5 (6)
Hypoprothrombinemia (prothrombin time > 20 seconds)	5 (6)
Hypoalbuminemia (< 3.5 g per 100 ml)	6 (7)
Hypochromic anemia (< 12 g per 100 ml) Macrocytosis in 1	5 (9)
Erythrocyte sedimentation rate (> 30 mm in 1 hour)	6 (9)

* Numbers in parentheses indicate number of patients examined or undergoing tests for the condition.



FIGURE 3 (*case 3*). Jejunal diverticulosis with malabsorption syndrome. Many large diverticula and disturbed mucosal pattern should be noted.

who had roentgenologic examination of the small bowel showed some evidence of a deficiency pattern. Frequent complications were perforation in four patients, obstruction in three, and hemorrhage in two. Ages at the time of diagnosis ranged from 30 to 65 with an average of 50 years. The symptoms at the time of diagnosis had been present one month to 27 years, and the patients lived two weeks to more than four years after the diagnosis was made.

JEJUNAL DIVERTICULOSIS

Numerous large diverticula of the small intestine, especially the jejunum, may be associated with macrocytic anemia or steatorrhea and other evidences of malabsorption (4, 28, 29). This condition is relatively rare. Discovery of diverticula in most cases has been incidental to the investigation of macrocytic anemia of obscure origin. Most of the patients are in the older age group and may give a long history suggestive of intermittent, partial obstruction of the small bowel or periodic diarrhea. Varying degrees of deficiency symptoms including neurologic defects may be observed.

CASE 3

A 72-year-old married white man was admitted June 2, 1958, because of hemoptysis two weeks previously and hoarseness for six months. Questioning revealed that he had suffered from diarrhea, weakness, fatigue, loss of weight, abdominal pains, and anemia for one and one-half years. His appetite had been good, but belching and occasional vomiting had been troublesome. He passed four to five stools daily which he described as loose, yellow, and foul-smelling. His usual weight was 146 pounds. The anemia had been treated with an iron preparation by mouth. He had never undergone any abdominal operation.

Physical examination disclosed a pale, thin man who weighed 136 pounds. The abdomen was moderately distended with visible peristaltic action and borborygmus. There were no neurologic abnormalities.

Laboratory studies revealed the following values: erythrocytes, 4,050,000, leukocytes 11,800/mm³ of blood; hemoglobin 12.3 g/100 ml. The blood smear showed macrocytosis, but the bone marrow was normocellular. The sedimentation rate was 58 mm in 1 hour by the Westergren method. The value for serum carotene was 22 international units/100 ml; for calcium, 9.3 mg, and for total proteins, 6.1 g with an albumin-globulin ratio of 3.4 : 2.7. The prothrombin time was 20 seconds (normal 16 to 19). Gastric analysis showed histamine-fast achlorhydria. Stools were collected for 72 hours while the patient was receiving a diet that contained 102 g of fat and 117 g of protein. Chemical analysis revealed a fecal excretion of 31.7 g of fat per day (46% of the total solids) and 4.3 g of nitrogen per day. Roentgenographic examination of the small intestine revealed many large diverticula of the jejunum, reduced motility, and a transit time compatible with some deficiency state (Figure 3). The roentgenogram of the thorax revealed a patchy pneumonitis in the left upper lobe, which disappeared during hospitalization.

Comment: In this case the malabsorption syndrome associated with jejunal diverticulosis consisted of mild macrocytic anemia and steatorrhea. Treatment con-

sisted of a nutritious, low-residue diet providing 80 g of fat per day; a multivitamin capsule daily, and 50,000 units of water-miscible vitamin A and 4 mg of vitamin K analog per week, and 30 μg of vitamin B_{12} administered subcutaneously each month. Satisfactory progress has been noted. Sometimes periodic administration of a tetracycline antibiotic is helpful (28). Resection of the offending loop of bowel containing the diverticula also has relieved the steatorrhea (29).

EFFECT OF ANTIBIOTICS ON ABSORPTIVE DEFECTS

The effect of neomycin, in a dosage of 1 g by mouth four times daily, and of oxytetracycline (Terramycin), 0.5 g four times daily, on the absorption of vitamin B_{12}, fat, and protein was studied in this patient. He was observed in a special metabolic hospital unit where accurate collections of stools and urine could be made while he was on the test diet mentioned above. The fat and nitrogen in the feces were determined by chemical analysis. Absorption of vitamin B_{12} was measured by giving an oral test dose of about 0.6 μg of cobalt^{60}-labeled vitamin B_{12}, representing about 0.5 μc, followed in two hours by a parenteral-flushing dose of 1,000 μg of nonradioactive vitamin B_{12}. Then the amount of radioactivity appearing in the urine in 22 hours was determined. The results were expressed in percentage of the oral dose; the normal quantity exceeds 8% (28).

The urinary excretion of vitamin B_{12} was 2% initially and 1% when the test was repeated using intrinsic factor (Figure 4). When repeated without intrinsic factor, none appeared in the urine. After a three-day course of neomycin the excretion increased to 6%. This was not improved after three or six days of treatment with oxytetracycline as usually occurs.

Fecal excretion of fat of 31.7 and 32.3 g per day in two control periods was decreased only slightly to 25 g per day during a three-day course of neomycin (Figure 4). This was followed by a period of anorexia, nausea, and diarrhea so that the study was discontinued for six days until the patient's eating and bowel habits were back to normal. The fecal excretion of fat decreased to 14.7 g per day during the first three-day course of Terramycin and to 12.3 during a second course. In a final control period the fecal excretion of fat increased to 25.3 g per day. Similar changes in fecal excretion of nitrogen were noted. Control values of 4.3 and 3.7 g per day decreased to 2.7 with neomycin, to 1.5 and 1.7 with oxytetracycline, and increased to 3.1 g per day during the final control period.

These observations add further credence to the belief that both steatorrhea and impaired vitamin B_{12} absorption are re-

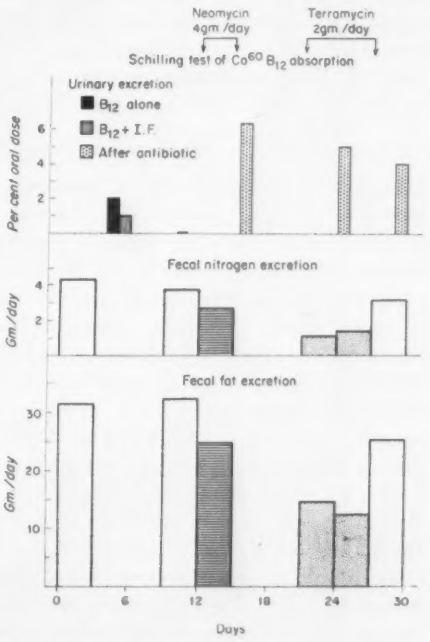


FIGURE 4 (*case 3*). Results of Schilling test of cobalt^{60}-vitamin B_{12} absorption, fecal excretion of nitrogen, and fecal excretion of fat before, during, and after courses of neomycin and oxytetracycline.

TABLE 5. Malabsorptive Defects for Fat and Cobalt^{60}-labeled Vitamin B_{12}

Case	Macrocytic Anemia	Steatorrhea	Clinical Condition	Urinary Excretion, Per Cent of Dose of Co^{60}-B_{12} Given		
				Alone	Plus Intrinsic Factor	After Tetracycline*
3	+†	+	Jejunal diverticulosis	2	1	5
4	+	0†	Jejunal diverticulosis	0	0	13
5	+	+	Jejunal diverticulosis	0	1	10
6	0	+	Jejunal diverticulosis	0	2	4
7	0	—	Jejunal diverticulosis	2	5	31
8	0	0	Jejunal diverticulosis	5	9	—
9	0	+	Nontropical sprue	3	3	4
10	+	—	Pernicious anemia	1	10	3
11	0	0	Healthy	21	21	19

* 2 g daily for 3 or 4 days.
† Symbols: +, present; 0, absent; −, not tested.

lated to an abnormal bacterial flora in the diverticula, competing in some way for these substances or interfering otherwise with absorption. Other possible causes of impaired absorption of fat are partial obstruction, altered motility, loss of absorptive surface due to the diverticula, and possibly spruelike changes in the remaining mucosa of the small intestine.

FAT AND VITAMIN B_{12} ABSORPTIVE DEFECTS

The extent and variability of absorptive defects for fat and vitamin B_{12} of six patients (Cases 3 to 8) with extensive jejunal diverticulosis are contrasted with those of a patient having nontropical sprue (Case 9), one ill with pernicious anemia (Case 10), and a healthy person (Case 11) in Table 5. Patients with multiple jejunal diverticula may have either macrocytic anemia or steatorrhea alone or in combination, or neither of these defects. Patients 4 and 5 showed the characteristic pattern of vitamin B_{12} absorption, that is, impaired absorption when cobalt^{60}-labeled B_{12} was given alone or with intrinsic factor but normal absorption after a course of tetracycline antibiotic. Patient 7 showed this response but did not have macrocytic anemia; perhaps the intake of vitamin B_{12} was adequate to offset impaired absorption. Patients 3 and 6 showed responses characteristic of about 80% of patients with nontropical sprue (Patient 9). The response of Patient 8 resembled that of Patient 10 who had pernicious anemia in respect to the response of improved absorption to added intrinsic factor, but Patient 8 did not have macrocytic anemia. In a healthy person the vitamin B_{12} absorption remained normal under all conditions.

GASTROJEJUNOCOLIC FISTULA

Internal fistulas, such as gastrojejunocolic (31), gastrocolic, or enterocolic fistulas (38), may produce a malabsorption syndrome. Only gastrojejunocolic fistulas will be considered in this report. A gastrojejunocolic fistula most often follows posterior gastroenterostomy which has been complicated by marginal ulceration. The main diagnostic features include prevalence in middle-aged men, previous gastroenterostomy, persistent diarrhea which may be lienteric, feculent belching or vomiting, and loss of weight preceded by pain or other symptoms of marginal ulceration. The majority of these patients probably have a definite malabsorption syndrome or varying degrees of nutritional deficiency, but these are often overlooked

in the process of diagnostic evaluation or the sense of urgency for surgical treatment. The manifestations of this disorder are due to passage of colonic bacterial contents into the stomach and jejunum with resultant inflammation and altered intestinal motility and absorption (31, 39). The lesion is demonstrated more often by roentgenographic study of the colon than of the stomach (40). Treatment involves correction of gross nutritional defects, preparation of the colon for surgery, and surgical removal of the fistula and old anastomosis with adequate gastric resection and establishment of continuity with the intestine.

CASE 12

A 57-year-old married white man was admitted September 8, 1957, because of diarrhea for the preceding eight weeks. A posterior gastroenterostomy for duodenal ulcer had been established in 1938. In addition to watery diarrhea, he had noted feculent belching, borborygmus, sore tongue, and a 28-pound weight loss in the past one and one-half years. In 24 hours he passed seven to eight stools which were watery, yellowish, and malodorous.

Physical examination revealed a thin man weighing 145 pounds who had a smooth red tongue. There were no abdominal findings except a previous operative scar.

Laboratory studies yielded the following values: erythrocytes, 4,600,000, leukocytes, 6,500/mm^3, and hemoglobin, 13 g/100 ml. The sedi-



FIGURE 5 *(case 12)*. Gastrojejunocolic fistula (arrow) with malabsorption syndrome. Filling of colon, small bowel, and stomach on roentgenologic study of the colon should be noted. (Reproduced by permission of *Postgrad. Med.* 26: 340, 1959.)

TABLE 6. The Findings and Malabsorptive Defects in Five Patients with Gastrojejunocolic Fistula and a Malabsorption Syndrome

Finding or Defect	Cases*
Diarrhea	5 (5)
Loss of weight (avg 28 pounds)	5 (5)
Feculent belching	3 (5)
Steatorrhea (> 7.5 g per day) Fecal fat (25–83, avg 46 g per day) (37–67, avg 49% of solids)	5 (5)
Azotorrhea (> 2.5 g per day) Fecal nitrogen (3.1–5.2, avg 4.1 g per day)	3 (3)
Hypocarotenemia (< 40 IU per 100 ml)	2 (2)
Hypocalcemia (< 9.2 mg per 100 ml)	1 (3)
Hypoprothrombinemia (prothrombin time > 20 seconds)	0 (4)
Hypoalbuminemia (< 3.5 g per 100 ml)	2 (5)
Hypokalemia (< 4.0 mEq per liter)	3 (3)
Hypochromic anemia (< 12 g per 100 ml)	0 (5)
Erythrocyte sedimentation rate (> 30 mm in 1 hour)	1 (3)

* Numbers in parentheses indicate number of patients examined or undergoing tests for the condition.

mentation rate was 17 mm in 1 hour by the Westergren method. The value for serum carotene was 10 international units/100 ml; for calcium, 9.6 mg; for phosphate, 2.5 mg; for total proteins, 4.6 g/100 ml with an albumin-globulin ratio of 3.8 : 0.8, and for potassium, 3.1 mEq/liter. The prothrombin time was 18 seconds (normal) and the gastric contents showed a total acidity of 54 units. The stool, while the patient was receiving a diet of unknown fat content, contained 37.9 g of fat per day (49.4% of the total solids) and 4 g of nitrogen per day. Roentgenologic study showed large gastric rugae and a gastrojejunocolic fistula (Figure 5).

Comment: This case represents the typical course of events in a patient with a gastrojejunocolic fistula and an associated malabsorption syndrome. Treatment consisted of partial gastrectomy and partial duodenectomy with a Billroth I anastomosis, resection of a portion of the jejunum with end-to-end jejunojejunostomy, and closure of the fistula. Progress was satisfactory, and nine months later the patient weighed 164 pounds and was having no difficulty with diarrhea or a dumping syndrome.

MALABSORPTIVE DEFECTS IN FIVE CASES

The main symptoms and laboratory tests in five patients with a gastrojejunocolic fistula and malabsorption syndrome, including Case 12, are listed in Table 6. Diarrhea, loss of weight, and feculent belching were all common. Rather marked steatorrhea was present in all cases, and mild azotorrhea, hypocarotenemia, and hypokalemia were prominent when tests were made. The other abnormalities listed occurred only infrequently, and significant anemia or hypoprothrombinemia did not occur. The erythrocyte sedimentation rate was seldom elevated. The severity and diversity of findings make it important to look for evidence of malabsorption in patients suspected of having a gastrojejunocolic fistula. Fortunately the incidence of such fistulas is decreasing.

COMMENT

The incidence of a malabsorption syndrome in the various diseases or conditions of the small intestine or mesentery under consideration is variable. Most patients

with Whipple's disease have a malabsorption syndrome, but occasionally other symptoms are manifested instead. Only a small portion of patients with lymphoma have a malabsorption syndrome, whereas the majority of patients with regional enteritis will show varying degrees of malabsorptive defects. Probably the incidence is greater than is suspected, because minor defects may be missed in the course of diagnosis and treatment of the primary condition. It is interesting to speculate why a malabsorption syndrome does not develop in all patients with these various diseases. Whether such a syndrome develops may depend on susceptibility and, in some instances, on whether the patient may have subclinical sprue, which becomes evident only with the onset of the superimposed disease.

The main problem in differential diagnosis is to distinguish between nontropical sprue and the various secondary malabsorption syndromes of intestinal origin. Symptoms and findings of abdominal distress, fever, an abdominal mass, sudden onset, and progression, in a patient in an older age group, should suggest a secondary condition. The roentgenologic examination of the small intestine will often give a clue as to the diagnosis. The changes shown in the roentgenograms (Figures 1 to 3, and Figure 5) would not have been confused with the deficiency pattern usually seen in sprue. However, such a pattern may be seen in lymphoma, regional enteritis, Whipple's disease, amyloidosis, scleroderma, and possibly other conditions. Peroral intubation biopsy of the jejunal mucosa using some modification of the Shiner tube (41) or the Crosby capsule (42) may be helpful. A characteristic change of the mucosa has been described in sprue. Amyloidosis and Whipple's disease may be detected in this manner. The changes in regional enteritis, lymphoma, and other conditions are less specific. Abdominal exploration or biopsy of a peripheral lymph node may be necessary to establish the diagnosis in some secondary forms.

The treatment of secondary malabsorption syndromes is often less successful than in nontropical sprue. A nutritious, low-residue, fat-restricted diet and supplementation with appropriate vitamins and minerals are necessary supportive measures. A gluten-free diet is seldom helpful. Adrenal steroids, antibiotics, nitrogen mustard, or roentgen therapy may be indicated as specific therapy. Some of the conditions may require surgical correction of the defect. In general, the prognosis is not as favorable in the secondary as in the primary malabsorption syndromes of intestinal origin.

Summary

Malabsorption syndromes include all of the diseases or conditions associated with impaired absorption from the small intestine. They include primary and secondary intestinal syndromes and malabsorption of gastric, pancreatic, or hepatobiliary origin. Recent observations in secondary intestinal malabsorption syndromes associated with amyloidosis, scleroderma, radiation enteritis, and Whipple's disease are discussed briefly. The main findings, and the malabsorptive defects of eight patients with regional enteritis, nine with lymphoma, six with jejunal diverticulosis, and five with a gastrojejunocolic fistula are described, and one case of each type is reported in detail. The variable incidence of a malabsorption syndrome associated with these conditions is discussed. Roentgenologic examination of the small intestine, peroral jejunal mucosal biopsy, or abdominal exploration may be necessary to distinguish these diseases from nontropical sprue. Treatment consists of correcting deficiency states by diet and replacement of vitamins and minerals. Adrenocortical steroids, roentgen therapy, or surgical procedures may be indicated in some diseases

producing secondary malabsorption syndromes.

Summario in Interlingua

Syndromes de malabsorption include omne le morbos e conditiones associate con imperfecte absorption ab le intestino tenue. Illos include primari e secundari syndromes intestinal e malabsorption de origine gastric, pancreatic, e hepatobiliari. Es discutite brevemente recente observationes in secundari syndromes de malabsorption intestinal associate con amyloidosis, scleroderma, enteritis de radiation, e morbo de Whipple. Es describite le major constatationes e le defectos malabsorptive de octo patientes con enteritis regional, de novem con lymphoma, de sex con diverticulosis jejunal, e de cinque con fistulas gastrojejunocolic. Un caso de cata un de iste typos es reportate in detalio. Es discutite le variabile incidentia de syndrome de malabsorption associate con iste conditiones. Examines roentgenologic del intestino tenue, peroral biopsia de mucosa jejunal, o exploration abdominal es possibilemente necessari pro differentiar inter iste morbos e sprue nontropic. Le tractamento consiste in corriger statos de carentia per le dieta e per le reimplaciamento de vitaminas e minerales. Steroide adrenocortical, roentgeno-therapia, o interventiones chirurgic es possibilemente indicate in certes del morbos que produce secundari syndromes de malabsorption.

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Plasma Fibrinogen in Familial Mediterranean Fever

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A RISE IN THE PLASMA FIBRINOGEN level is a nonspecific body response which occurs in many pathological states, resembling in this respect an increase in the erythrocyte sedimentation rate. Indeed, the fibrinogen level is one of the principal factors influencing the erythrocyte sedimentation rate (1). Little is known of the mechanism which controls the fibrinogen level in health and disease, or of the possible functions of fibrinogen other than its role in blood clotting. The possibility of qualitative differences in the fibrinogen in various disorders has hardly been explored, most studies having been concerned only with quantitative aspects.

Sometimes the rise in the plasma fibrinogen level is considerable. Abnormal levels, higher than 900 mg/100 ml and occasionally even above 1,300 mg/100 ml, have been observed in lobar pneumonia (2–4), bronchial carcinoma (2, 4), nephrosis (1, 2), amyloidosis (1, 2), uremia (5), subacute bacterial endocarditis (1, 5), rheumatoid arthritis (6–8), pericarditis (5), myocardial infarction (9–14), pulmonary infarction (4, 5), and thrombophlebitis (1). When high plasma fibrinogen values were found by us in familial Mediterranean fever, it seemed worth-while to collect more information on the behavior of fibrinogen in this disease.

Studies of fibrinogen levels in familial Mediterranean fever should be of interest for several reasons:

1. Familial Mediterranean fever, a genetic disease with autosomal recessive inheritance, provides within itself a variety of clinical states for comparative investigation, its clinical picture being characterized by irregularly recurring attacks of fever accompanied by pain in the chest, abdomen, skin, and joints (15, 16).

2. Amyloidosis, in itself associated with hyperfibrinogenemia (1, 2, 17, 18), has been demonstrated to have a high incidence in familial Mediteranean fever, appearing as an independent, genetically-determined character (19).

3. A fibrillar component of unknown nature, of dimensions comparable to those of fibrinogen, has recently been described in human and experimental amyloidosis (20, 21).

The following reports our observations of patients with familial Mediterranean fever.

METHODS

Fibrinogen determinations were made by the gravimetric method of Gram (22) as modified by Schultz (2), or by the colorimetric method of Mizuta (23), as cited and modified by Rappaport and Loew (24).

To compare these methods, the results of 164 determinations done simultaneously by the two methods were correlated and the following regression formula was computed: $G = 0.75C + 21$, where G is the value obtained by gravimetry, expressed in milligrams per 100 milliliters of plasma, and C the analogous value obtained by colorimetry. These determinations, as well

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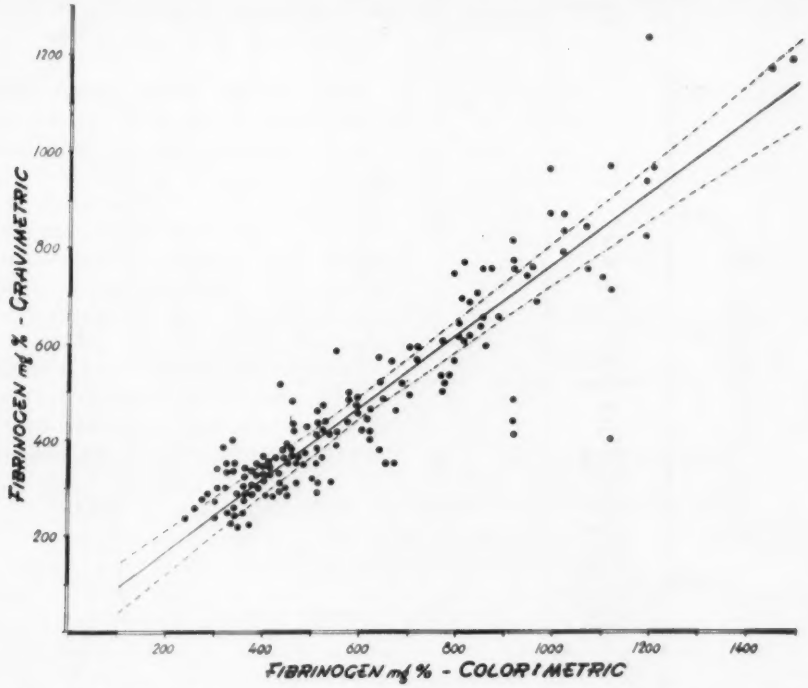


FIGURE 1. Correlation between gravimetric and colorimetric fibrinogen determinations. Scatter diagram of 164 simultaneous fibrinogen determinations. The solid line represents the regression line; the broken lines represent the limits of confidence (95%).

as the regression line and its limits of confidence fitted to them, are shown in Figure 1. This demonstrates that the results are comparable, and in this paper all fibrinogen values will be given as "gravimetric" values.

MATERIAL

The normal range of plasma fibrinogen levels was determined by examining 50 healthy members of the hospital staff. All were in the age group below 35, as were most of the patients with familial Mediterranean fever who constitute this series.

In 71 patients suffering from this disease, as defined by Heller, Sohar, and Sherf (16), plasma fibrinogen levels were determined on 246 occasions, often on several successive days.

RESULTS

PLASMA FIBRINOGEN LEVELS IN NORMALS

Normal values ranged from 186 to 394 mg/100 ml. The mean was 286 mg/100 ml

TABLE 1. Frequency Distribution of Plasma Fibrinogen Determinations in Familial Mediterranean Fever

Value (mg/100 ml)	Determinations	
	Number	Per Cent
Below 382 (normal range)	29	11.8
383– 600	112	45.5
600– 800	71	28.7
800–1,000	21	8.6
1,000–1,200	8	3.3
1,200–1,600	5	2
Total	246	100

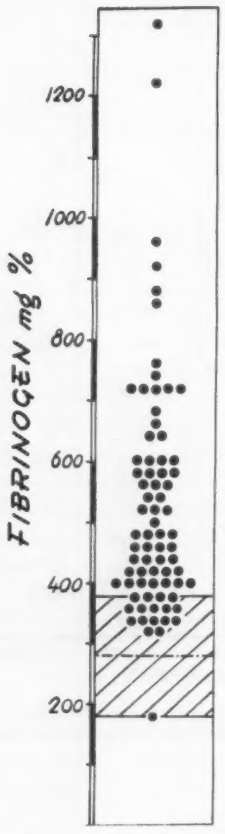


FIGURE 2. Plasma fibrinogen levels of patients free of attacks for eight days or more. The hatched area represents the normal range (mean, ±2 SD).

and the SD ±50. These results are in accordance with those reported in the literature for this age group (1, 2, 25, 26).

PLASMA FIBRINOGEN LEVELS IN FAMILIAL MEDITERRANEAN FEVER

The frequency distribution of all 246 plasma fibrinogen determinations performed on patients with familial Mediterranean fever is given in Table 1. Eighty-eight per cent fell above the normal range, the majority being between 400 and 800 mg/100 ml. Only 12% fell within the normal range. These normal values were obtained in 18 patients, of whom 17 showed elevated plasma fibrinogen levels in other determinations which are included in this series.

Since familial Mediterranean fever is characterized by recurrent attacks involving the abdomen, chest, or joints, and by the development of amyloidosis (16), we shall present these determinations in relation to (a) the interval between attacks, (b) the brief abdominal and chest attacks, (c) the more prolonged attacks in joints, and (d) the amyloid nephropathy of familial Mediterranean fever (19).

1. *Plasma Fibrinogen Levels in the Interval Between Attacks:* Intervals between attacks may vary from a few days to several months. In order to obtain the basic values

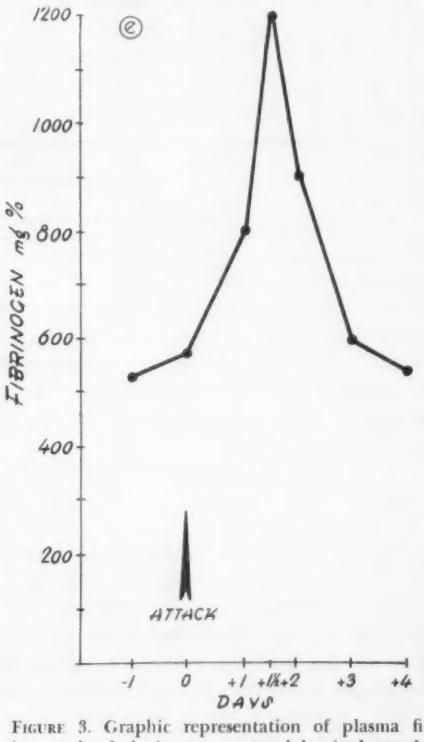


FIGURE 3. Graphic representation of plasma fibrinogen level during an acute abdominal attack. (This patient was hospitalized after the close of the series reported in this paper.) On day +1 plasma fibrinogen determinations were done twice, in the morning and in the evening.

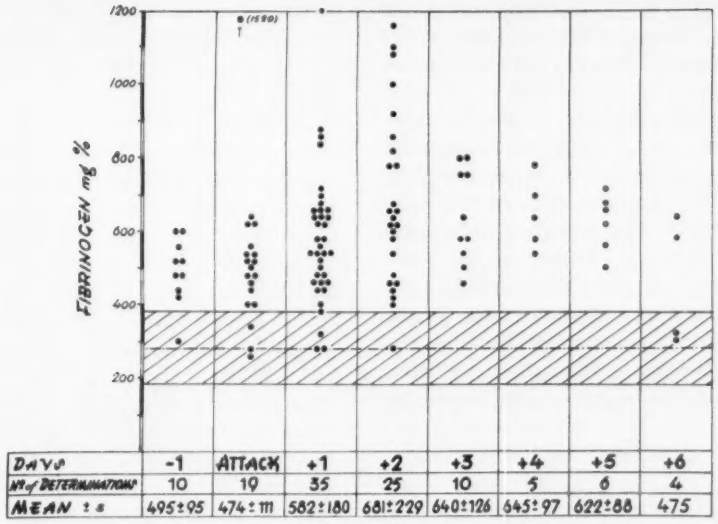


FIGURE 4. Plasma fibrinogen levels during acute attacks involving abdomen and chest. The hatched area represents the normal range (mean, ±2 SD).

of plasma fibrinogen in familial Mediterranean fever, unaffected by a recent attack, only the 75 determinations performed at least eight days after an attack are included here. Some of the patients had been free from attacks for many months. The results are shown in Figure 2. It is evident that almost all of the values are considerably elevated above the upper limit of normal, thus demonstrating that basal plasma fibrinogen levels in this disease are high.

2. *Plasma Fibrinogen Levels During Attacks Involving Abdomen and Chest:* Under ideal conditions the study of the relationship between plasma fibrinogen levels and attacks should be based upon daily plasma fibrinogen determinations, in order to include both an attack and the periods preceding and following it. For understandable reasons, this ideal was approached only in a minority of cases. A typical result is shown in Figure 3. The elevated base line plasma fibrinogen level rose after the attack, reached peak values in 24 to 72 hours, and returned to the base line on or about the sixth day after the onset.

Figure 4 is a daily graphic representation of all plasma fibrinogen determinations performed from the day preceding an attack to six days after its onset, including cases in whom only few determinations were available. The mean values for each day are also noted. This "average" curve is of the same pattern as that described above.

Variations were observed between different patients, as well as between different attacks in the same patient, but these were all within the described pattern. In no case was the fibrinogen level found to rise *prior* to the onset of the attack.

3. *Plasma Fibrinogen Levels in Attacks Involving Joints:* As previously stated, attacks in joints often last longer than one or two days; they may last for weeks. It seemed impractical, therefore, to correlate values with the day of onset of an attack. Forty-three plasma fibrinogen level determinations obtained on 13 patients during an attack involving joints are included in Figure 5. All of these values were considerably elevated above the upper limit of

normal, and most of them were above the basal plasma fibrinogen levels observed between attacks of familial Mediterranean fever (Figure 2).

In a few instances of brief joint attacks, plasma fibrinogen levels were determined daily. It appeared that the plasma fibrinogen curve in joint attacks is of the same pattern as that found during abdominal and chest attacks. Comparing the individual curves in abdominal attacks with those obtained in attacks involving joints, as well as the determination shown in Figure 5 with the one in Figure 3, it is obvious that plasma fibrinogen levels frequently attain higher peaks in joint attacks than in abdominal or chest attacks.

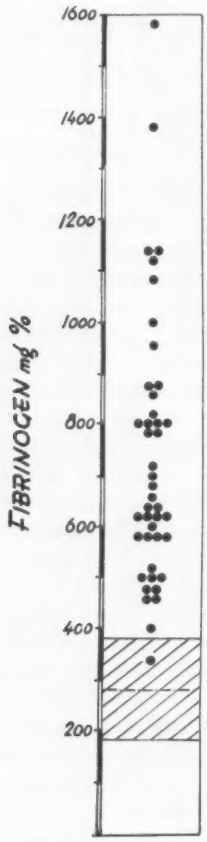


FIGURE 5. Plasma fibrinogen levels during acute attacks involving joints (43 determinations on 13 patients).

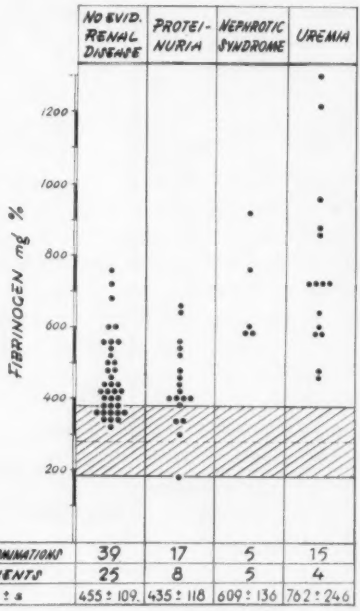


FIGURE 6. The relation of plasma fibrinogen levels to the nephropathy of familial Mediterranean fever.

4. *Plasma Fibrinogen in Amyloid Nephropathy of Familial Mediterranean Fever:* Amyloidosis with progressive kidney involvement is a genetically determined, independent character of familial Mediterranean fever which, to date, has made its appearance in 30% of our patients (19). Our patients can be separated into four groups: (a) those without clinical evidence of renal disease; (b) those with proteinuria; (c) those with the nephrotic syndrome; (d) those with uremia.

Figure 6 shows the plasma fibrinogen values obtained in each of these groups. Only interval values (determined at least eight days after onset of an attack) were included, in order to exclude the temporary influence of a recent attack.

It is evident that the plasma fibrinogen values in the groups suffering from the nephrotic syndrome and from uremia are

considerably higher than are the values obtained in the groups without renal disease or with only proteinuria.

Discussion

The observations reported above show that elevation of the plasma fibrinogen level is the rule in familial Mediterranean fever. Extreme elevations, i.e., above 1,200 mg/100 ml, proved to be rare, and usually occurred in the late stages of amyloid nephropathy.

For purposes of differential diagnosis the plasma fibrinogen level is of no value insofar as joint attacks are concerned, since high plasma fibrinogen levels are common in chronic rheumatoid arthritis (6–8) and in other conditions in which joint lesions are prominent symptoms (27–29). In the differential diagnosis of chest and abdominal attacks, values above 800 mg/100 ml may support the diagnosis of familial Mediterranean fever in a clinically suggestive case. Acute abdominal emergencies such as appendicitis (1) cholecystitis (2), and pancreatitis (30) do not, as a rule, show such high levels. On the other hand, a repeatedly normal plasma fibrinogen level in a clinically doubtful case could tend to weaken the diagnosis of familial Mediterranean fever.

The fact that fibrinogen levels rise above the base line after a time lag following the onset of the attack disproves the possibility that the rise in fibrinogen level is the factor provoking the attack.

The continuous elevation of the plasma fibrinogen level between attacks, even during prolonged remissions when the patient is clinically well and free of signs of renal involvement, is one of the important observations of this study. This finding suggests the continuous activity of some factor responsible for the high level of plasma fibrinogen during the remissions. Theoretically, the factor may be (1) related to the basic metabolic deviation of familial Mediterranean fever or (2) due to changes induced by the clinical manifestations. This problem cannot be solved on the basis of present knowledge, since there is no sign by which familial Mediterranean fever homozygotes may be recognized prior to the appearance of the clinical manifestations. The determinations of fibrinogen levels in asymptomatic members of familial Mediterranean fever sibships, which will occasionally contain preclinical homozygotes, and their long-term follow-up may possibly provide the answer.

The association between prolonged states of hyperfibrinogenemia and the development of amyloidosis is well known. This association has been reported in all forms of secondary amyloidosis (1, 2, 17, 18). In experimentally induced amyloidosis, Fendel and Gerok (31) have convincingly demonstrated that the chances of a mouse's developing amyloidosis depend upon whether or not it responds to a noxious agent (casein injection) by a rise in plasma fibrinogen. The amyloidosis of familial Mediterranean fever is another example of this intriguing association between hyperfibrinogenemia and amyloidosis. Before a reasonable theory of the relation between fibrinogen and amyloid can be formulated, more information is required than is now available.

In summing up, we may say that our results, considered in view of the background that has been reported on fibrinogen in other conditions, and especially taking into account the permanent elevation of the fibrinogen level in familial Mediterranean fever even during long remissions, seem to strengthen the impression that the behavior of fibrinogen in this disease (as in other diseases) reflects pathogenetic and pathophysiological relationships of significance. Further progress in the understanding of the metabolism and regulation of fibrinogen requires methods by which fibrinogen can be specifically characterized and differentiated and its rate of production and destruction deter-

mined. Familial Mediterranean fever seems to provide a natural experimental set-up for the study of these problems in man.

Summary

Two hundred forty-six plasma fibrinogen determinations were performed on 71 patients with familial Mediterranean fever.

Plasma fibrinogen determinations performed in the intervals between attacks showed values that were consistently elevated above the upper limit of normal.

After the onset of an attack, a further rise in the plasma fibrinogen was noted, which reached its peak after 24 to 72 hours and returned to the base line after six days. The rise of plasma fibrinogen in attacks involving joints was higher and of longer duration than that found in attacks involving abdomen or chest.

In the later stages (nephrotic syndrome and uremia) of the amyloid nephropathy of familial Mediterranean fever, the plasma fibrinogen level was considerably higher than in patients who had no clinical evidence of kidney disease or with proteinuria only. Values of 1,200 to 1,500 mg/100 ml were observed most often, though not exclusively, in the late stages of amyloid nephropathy.

Plasma fibrinogen determinations, though of no diagnostic value in attacks involving joints, may be of help in attacks affecting the abdomen or chest.

The relationship between hyperfibrinogenemia and amyloidosis, of which familial Mediterranean fever is another example, was noted.

Acknowledgment

We are indebted to Mrs. S. Klonski, M.Sc. and to Miss I. Zaharor for their able technical assistance; to D. Jaski, M.Sc., for the statistical comparison of the methods employed; and to J. Gafni, M.D., for his help in preparing this paper.

Summario in Interlingua

Febre mediterranee familial es un disordine genetic con complete hereditage autosomal recessive, manifeste clinicamente in duo independente characteristicas phenotypic: (1) Recurrente attaccos de febre accompaniate de dolor in le abdomine, le thorace, le pelle, o le articulationes; (2) amyloidosis que deveni le causa de disfallimento renal e morte a un precoce etate.

Viste le conception que febre mediterranee familial representa un innate error de metabolismo, il pareva essential investigar le alterationes in le proteinas del plasma, le plus obvie del quales es hyperfibrinogenemia. Duo centos quaranta-sex determinationes de fibrinogeno esseva effectuate in 71 patientes con febre mediterranee familial.

Determinationes del fibrinogeno del plasma, effectuate durante le intervallos inter le attaccos e mesmo durante prolongate remissiones, monstrava uniformemente valores elevate in supra del limites normal.

Post le declaration de un attacco il occurreva un elevation additional del nivello de fibrinogeno del plasma, attingente su maximo post inter 24 e 72 horas e retornante al linea de base post sex dies. Le augmento del fibrinogeno del plasma in attaccos afficiente le articulationes esseva plus marcate e plus prolongate que illo in attaccos afficiente le abdomine e le thorace.

In le stadios tardive (con syndrome nephrotic e uremia) del nephropathia amyloide de febre mediterranee familial, le nivellos de fibrinogeno del plasma esseva considerabilemente plus alte que in patientes sin signos clinic de morbo renal o con proteinuria sol. Valores de 1.200 a 1.500 mg per 100 ml esseva observate le plus frequentemente—sed non exclusivemente—in le stadios tardive de nephropathia amyloide.

Le association inter prolongate stadios de hyperfibrinogenemia e le disveloppamento de amyloidosis es ben cognoscite, tanto in amyloidosis secundari como etiam in amyloidosis experimental. Febre mediterranee familial es un exemplo de iste interessantissime association in casos de amyloidosis que es determinate geneticamente.

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Varicella Pneumonia

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PRIMARY VARICELLA PNEUMONIA has only recently been recognized as a serious and occasionally fatal complication of chickenpox in the adult. Waring, Neuberger, and Geever (1) reported the first fatal case in 1942. Since then, less than 100 cases have been reported, although some authors (2, 3) have pointed out that this complication is a more common occurrence than previously had been estimated. The purpose of this report is to add 13 cases to the literature, to emphasize that the incidence of pneumonia in adults with chickenpox is much higher than heretofore appreciated, and to point out the lack of correlation between clinical and X-ray findings.

Only 15 cases of chickenpox pneumonia had been reported up to 1956, and it was thought to be a rare complication of adult varicella. Frequent case reports have appeared in the literature in the past three years, either documenting a death or citing other complications of varicella or varicella pneumonia (4–6). This report comprises the largest series of cases to date and presents the highest incidence of pneumonia in varicella. It is also the only large series without a fatality.

METHODS AND MATERIAL

Thirty-eight adults with varicella were admitted to Meadowbrook Hospital in the period January, 1953, through July, 1960. Thirteen of the 38 had clinical or roentgenographic evidence of pneumonia, or both. The following four cases are illustrative.

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CASE 1

A 31-year-old Negro female developed a typical varicella eruption one day prior to admission. Cough and sore throat appeared the following day (April 2, 1953) and she was admitted to the hospital. She had no hemoptysis, chest pain, or shortness of breath. Her past medical history was noncontributory. One parent had tuberculosis.

Physical examination on admission revealed a well developed, well nourished Negro female in no distress. A rash typical of varicella covered her head and trunk, and there were pocks on the tonsils, palate, and buccal mucosa. The lungs revealed sonorous rhonchi. The chest film on admission (Figure 1) showed diffuse, mottled, punctate, granular densities scattered throughout both lung fields, predominantly on the right, with relative sparing of the apices and extreme bases. Subsequent X rays showed resolution, and the patient was discharged on April 11, 1953. Later admissions to the hospital for unrelated diseases disclosed no respiratory abnormalities.

Comment: This patient had minimal clinical symptoms consisting chiefly of a dry cough. Physical examination revealed only coarse rhonchi throughout the lung fields, yet she had marked X-ray findings which were typical of those seen in severe cases.

CASE 2

A 36-year-old white male first noted a chickenpox exanthem on April 13, 1956. He became febrile and on April 16 developed hemoptysis, cough, and extreme dyspnea, and was admitted to the hospital. Past medical history and review of systems was noncontributory.

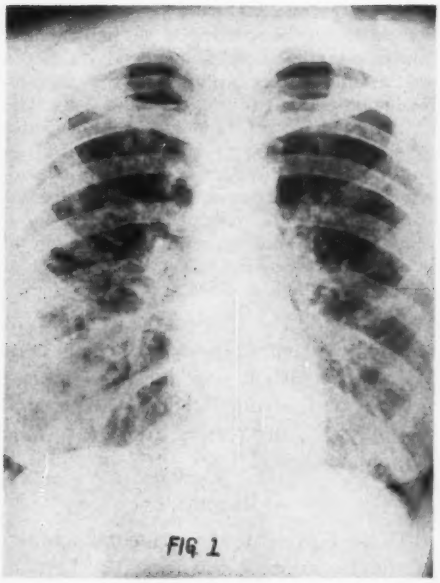


FIGURE 1. *Case 1.* Admission chest X ray of 31-year-old Negro female on April 2, 1953.

Physical examination on admission revealed an acutely ill white male in marked respiratory distress, with rapid, shallow respirations up to 72/min. He coughed up blood-tinged sputum during the examination. The pulse was 104/min, blood pressure, 120/70 mm Hg, temperature, 103 F. The pocks were in various stages of development and covered his entire body except for the palms and soles. The throat contained many pocks. The findings in the lungs were limited to occasional râles at both bases. A lumbar puncture was normal. Sputum studies revealed normal flora, and smears for tubercle bacilli were negative. A chest X ray on April 16 (Figure 2) revealed extensive patchy and confluent densities scattered throughout both lung fields, particularly in the left mid-lung area. The patient was treated with oxygen, vaporizers, intravenous fluids, penicillin, streptomycin, and sedation. He gradually improved and was discharged on April 24. Serial chest roentgenograms revealed clearing of the process and on April 30 showed no areas of pneumonitis. He returned to work without any sequelae two and one-half weeks after admission.

Comment: This patient was acutely ill and required almost constant attention from the hospital staff. The picture was similar to that seen in several of the fatal cases noted in the literature. Antibiotics were used for prophylaxis, but their effect on the outcome of this case was indeterminate.

CASE 3

A 36-year-old white male with a four-day history of varicella was admitted on March 18, 1955, because of possible secondary infection of the pocks, and because there were several children at home who were ill with chickenpox. Past medical history and review of systems were noncontributory.

Physical examination on admission revealed a well developed, well nourished white male, whose entire body was covered with a typical varicella eruption. Several of the pocks were pustular. The lungs were clear. Laboratory studies were unremarkable. X-ray examination on March 22, 1955, (Figure 3) revealed marked intensification of the vascular pattern throughout both lungs and patchy infiltration of the right upper lobe. The patient had no respiratory symptoms in the hospital and was treated with penicillin because of the secondarily infected pocks. Unfortunately, no follow-up X-ray examination was performed.

Comment: This was a case with a severe eruption and typical, though moderate,

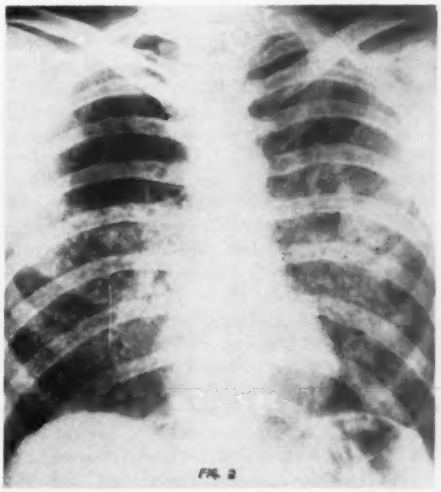


FIGURE 2. *Case 2.* Admission chest X ray of 36-year-old white male on April 16, 1956.

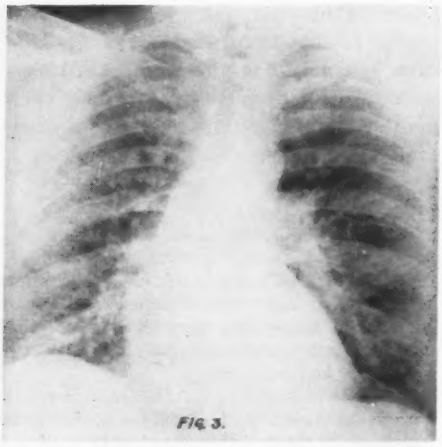


FIGURE 3. *Case 3.* Admission chest X ray of 36-year-old white male on March 22, 1955.

roentgenographic changes in the lungs. The patient had no respiratory symptoms despite the X-ray findings.

CASE 4

A 25-year-old white male was admitted to Meadowbrook Hospital on April 19, 1955, with a three-day history of varicella. On the day before admission, he had developed shortness of breath, anterior chest pain, and cough. Hemoptysis appeared on the day of admission. He had been a known diabetic for 14 years and had had paralytic poliomyelitis 11 years prior to admission, with residua in both legs and the left arm.

Physical examination on admission revealed a well developed, well nourished white male sitting upright in bed, with rapid, shallow respirations at 36/min. The pulse was 110/min, the temperature, 100.2 F, the blood pressure 108/70 mm Hg. There was flaring of the alae nasi. No cyanosis was noted. The trunk and extremities were covered by an extensive varicella eruption. There were fine, crepitant râles at both lung bases. Laboratory work was extensive because of complicating diabetic acidosis; however, except for hyperglycemia and electrolyte abnormalities, there were no abnormal findings of note. Studies for acid-fast bacilli were negative. A chest X ray on April 20 (Figure 4) revealed nodular, discrete, confluent densities scattered throughout both lung fields and extending to the periphery. The hilar regions were engorged. There was also demineralization of the bones in the left shoulder girdle and diminution in the musculature overlying the left half of the chest. Also noted was a mild rotary scoliosis of the thoracolumbar spine with convexity to the right. The latter changes were residua of poliomyelitis. Repeat chest films revealed clearing of the process, and on May 4 there was complete resolution of the pneumonic process. The patient was treated with oxygen, vaporizers, intravenous fluids, and penicillin, in addition to insulin. The respiratory symptoms cleared as the X-ray findings resolved.

Comment: This patient was acutely ill and required vigorous supportive therapy. He was potentially a seriously ill patient because of the complicating diabetes and loss of ventilatory reserve from the residua of poliomyelitis.

RESULTS

Table 1 presents the principal findings of the 13 patients who form the basis of this report. Their ages ranged from 20 to 47 years. None of the patients was markedly cyanotic, though seven required oxygen. One patient with secondary infection of the pocks had moderate leukocytosis. Despite frequent observations of rapid, shallow respirations and anxiety, physical findings of pneumonia were few. Three patients did not receive antibiotics. The others were treated with penicillin in combination with another antibiotic. Steroids were not used. Seven of the patients re-

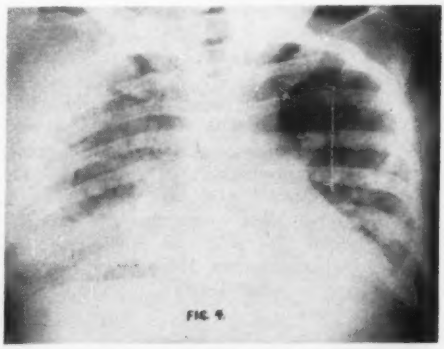


FIGURE 4. *Case 4.* Admission chest X ray of 25-year-old white male on April 20, 1955.

TABLE 1. Analysis of 13 Cases of Varicella Pneumonia at Meadowbrook Hospital, January, 1953, Through July, 1960 *

Case No. Age Sex Race	Onset of Pulmonary Symptoms after Rash	Resp. and Pulse on Adm.	Symptoms	Phys. Exam.	Antibiotics, Oxygen	Adm. WBC	Complications
1. 31 yr, N. F. Adm. 4/2/53 Dis. 4/11/53	1 day	P. 120 R. 25	Cough	Rhonchi	Pen.	5,200 54 N 25 L 18 M 3 E	None
2. 36 yr, W. M. Adm. 4/16/56 Dis. 4/24/56	3 days	P. 104 R. 72	Hemoptysis, dyspnea, pleuritic pain	Râles at bases	Pen. Strep. Oxygen	10,550 52 P 47 L 1 M	None
3. 36 yr, W. M. Adm. 3/18/55 Dis. 3/23/55	None	P. 100 R. 20	None	Normal	Pen.	13,100 45 N 44 L 10 M 1 E	None
4. 25 yr, W. M. Adm. 4/19/55 Dis. 4/25/55	2 days	P. 110 R. 36	Dyspnea, chest pain, hemoptysis	Râles at bases	Pen. Oxygen	6,800 55 N 41 L 4 M	Acidosis
5. 20 yr, N. F. Adm. 4/2/59 Dis. 4/8/59	None	P. 70 R. 20	None	Dry râles, rhonchi	None	7,550	None
6. 30 yr, W. M. Adm. 1/16/58 Dis. 1/27/58	3 days	P. 100 R. 44	Cough, dyspnea, chest pain	Scattered fine râles	Pen. Achro. Oxygen	9,900 79 N 21 L	Possible peptic ulcer
7. 33 yr, W. M. Adm. 5/16/58 Dis. 5/23/58	3 days	P. 100 R. 26	Cough, hemoptysis, dyspnea	Dry râles, rhonchi	Pen. Chloro. Oxygen	9,900 49 P 50 L 1 M	None
8. 25 yr, W. F. Adm. 2/5/59 Dis. 2/11/59	2 days	P. 120 R. 44	Cough, dyspnea, chest pain	Moist râles at bases	Achro. Oxygen	5,900 46 P 52 L 2 M	Otitis media. Pregnant (middle trimester)
9. 23 yr, W. M. Adm. 5/6/58 Dis. 5/19/68	2 days	P. 94 R. 22	Cough, chest pain	Dullness right apex	Pen. Chloro. Oxygen	7,200 50 P 50 L	None
10. 26 yr, W. M. Adm. 2/2/54 Dis. 2/9/54	Same day as rash	P. 100 R. 28	Cough, dyspnea	Normal	Aureo. Oxygen	4,650 62 P 33 L 3 M 2 E	None

* Legends for symbols: N.F.: Negro female; W.M.: white male; W.F.: white female. N = neutrophils; L = lymphocytes; M = monocytes; P = polymorphonuclears; E = eosinophils.

TABLE 1. (*Continued*)

Case No. Age Sex Race	Onset of Pulmonary Symptoms after Rash	Resp. and Pulse on Adm.	Symptoms	Phys. Exam.	Antibiotics, Oxygen	Adm. WBC	Complications
11. 47 yr, N. F. Adm. 3/21/60 Dis. 3/26/60	None	P. 96 R. 18	None	Normal	None	4,200 45 P 51 L 3 M 1 E	Abnormal ECG
12. 32 yr, W. M. Adm. 4/10/60 Dis. 4/20/60	Same day	P. 100 R. 20	Cough (dry)	Scattered wheezes	None	8,600 41 P 59 L	None
13. 32 yr, W. M. Adm. 7/10/60 Dis. 7/16/60	3 days	P. 118 R. 20	Cough	Moist râles and wheezes	Pen.	9,100 78 P 21 L 1 M	None

ceiving oxygen also required intravenous fluids. Shock was not present in this series and involvement of other organs was rare. Three patients had lumbar punctures, but all the spinal fluid specimens were normal. All patients had nose, throat, and blood cultures, and where sputum was raised, this was cultured. All the studies were unremarkable. Two patients were readmitted later for unrelated illnesses, and no respiratory sequelae of any significance were noted.

The X-ray appearance did not correlate with the clinical picture in Cases 1, 11, and 12, who had typical roentgenographic findings but little clinical distress. Cases 1, 3, 11, and 12 would not have been diagnosed as having varicella pneumonia unless X rays had been taken. This leads to the conclusion that other cases may be missed and that many patients with mild or minimal respiratory symptoms are probably treated at home without recognition of the pulmonary involvement. In support of this statement, it is to be noted that 12 of the 38 persons admitted to Meadowbrook Hospital during this period had no chest X rays.

One can conclude that the occurrence of pneumonia complicating adult varicella is higher than previously expected. Instead of finding this complication in approximately 34% of all patients, if one only considers the 26 who had chest films the incidence would be 50%. This high figure is in agreement with the observations of Krugman, Goodrich, and Ward (2) and of Fitz and Meiklejohn (3) that this complication is more common than was previously thought.

DISCUSSION

Varicella pneumonia may be very mild with few respiratory symptoms, or it may be severe with marked cyanosis, dyspnea, and tachypnea, and may terminate fatally. The pneumonia usually occurs between the second and the sixth day of the illness and predominantly affects adults. It begins with a cough and mild shortness of breath. Within 24 to 48 hours, it may become a fulminating process with the patient in extremis. The physical findings in the lungs are usually minimal, in comparison with the severity of the illness, and some authors have noted that at least 50% of cases present with chest pain (2, 3, 7). Six of the patients in our series had this symptom during the course of their illness. Hemoptysis is often present and cyanosis

may be severe. Other organs may be involved. Adrenal insufficiency may occur (8), as well as pericarditis, encephalitis, and nephritis. Rapid, shallow respirations and marked anxiety were noted in several of the subjects comprising this report. Shock may occur, and fatal cases often terminate with pulmonary edema. Most patients will recover without any sequelae, and improvement is noted within a few days. The majority are better within one week. Clinical improvement usually parallels the subsidence of the rash. The more severe pneumonic processes have been associated with a widespread hemorrhagic, confluent rash, but blood studies on these patients failed to reveal any clotting deficiencies (9, 10). All of the cases requiring oxygen in our series had widespread rashes.

The hemogram, urinalysis, and blood chemistries are usually normal. The urine may reveal changes secondary to dehydration but is otherwise normal. Blood cultures are sterile, and the sputum and nose and throat cultures usually reveal normal flora. The routine agglutination tests are normal, and the electrocardiogram should be normal unless pericarditis, myocarditis, or an electrolyte imbalance is present.

The chest X ray is the most impressive abnormal finding. The roentgenographic appearance in the usual case is that of a diffuse dissemination of punctate and small nodular densities throughout both lungs, with relative sparing of the apices. Several areas may show conglomerate patches, though these are rarely greater in area than 0.5 cm. Radio-opacity is usually heaviest in the perihilar regions, where strandlike densities blend with slightly prominent hilar nodes (9–16). The process shows regression within one week and usually completely clears within two weeks.

Varicella pneumonia has been described by several authors as being viral in nature, and autopsy studies have demonstrated that the pneumonia is due to the virus of chickenpox. Present techniques cannot differentiate between the virus of varicella and herpes zoster (4, 5, 17–21). Claudy (20) reported a fatal case in which, at autopsy, the striking gross feature was the presence of varicella pocks on the pleura, within the pulmonary parenchyma, and on other organs. Frank (4) noted that the pneumonia could not be differentiated grossly from other forms of viral pneumonitis. The picture was that of a patchy bronchopneumonia, with areas of consolidation and tendency toward confluency and suppuration. Microscopically, lobular consolidation was found, and the alveoli contained exudate of red cells, fibrin, and mononuclear cells. Characteristic type A inclusion bodies were identified in the mononuclear cells of the pulmonary exudate, as noted by Krugman et al. (2) and by Frank (4). The cases that were autopsied also revealed widespread involvement of all the organs (2–5, 7, 19, 20). These observations are in disagreement with the original report of Bullowa and Wishak (22), who noted a very low incidence of pneumonic complications (0.8%) in their series and did not describe the fulminant varicella pneumonia that we are discussing today. They concluded that the pneumonia was streptococcal in origin.

Treatment is supportive. Most authors use antibiotics in various combinations to prevent or to treat presumed secondary infection (23). Fitz and Meiklejohn (3) treated several cases without antibiotics and noted no difference in the outcome.

Fluid and electrolyte therapy is essentially a matter of maintaining proper hydration and of replacing electrolyte deficits in cases of vomiting; it is usually reserved for the more severe cases.

Oxygen is of great value in combating cyanosis. Rosecan, Baumgarten, and Charles (6) treated severe cyanosis in one of their patients with an oxygen mask inside the oxygen tent. Thus, the leaks in the mask were plugged by a high oxygen

atmosphere. Cold steam vaporizers also are supportive therapy. DeMase, Gravio, and Allen (24) used a respirator with success to combat cyanosis and to increase ventilation.

There is some controversy over the use of steroids. Several authors have reported fatal cases of chickenpox in children who were treated with steroids and noted that the disease was more severe in patients receiving this therapy (25, 26). Gable (27) thought the increased susceptibility of pregnant women or the immediate postpartum female to viral disease might be accounted for by the increased steroid secretion during pregnancy. Recent reports of fatalities in pregnant women may support this thesis (28, 29). However, other authors feel that steroids are justified in the severe cases, since autopsy evidence has shown adrenal involvement (8). Despite the altered immune responses that may occur with steroids, this therapy is probably indicated where there is evidence of adrenal collapse or when the outcome is in doubt. Nevertheless, one must point out that the final place of corticosteroids in treatment remains to be clearly demonstrated.

Mortality rates vary. Death may occur at any time, and there are few criteria that one can use to judge which cases will be "severe." The prognosis is graver as more organ systems are involved and when concomitant disease is present. The majority of patients recover without sequelae. It seems that varicella pneumonia complicating pregnancy has the poorest prognosis (28, 29). One of our patients (Case 8) was in the middle trimester of pregnancy, but signed her release during her hospitalization when she became asymptomatic and was lost to follow-up.

Summary

Thirteen of 38 adult patients admitted to Meadowbrook Hospital because of varicella from January, 1953, through July, 1960, had clinical or roentgenographic evidence of pneumonia, or both. Four of the cases were asymptomatic and were diagnosed from X-ray findings alone. In 12 of the 38 patients no chest films were taken. It is possible that the true incidence of this complication is close to 50% of all cases of adult varicella.

Treatment and prognosis have been discussed and the potential severity of this complication is again noted. No deaths occurred in this series, though several of the patients were seriously ill, and corticosteroids were not used.

The roentgenographic appearance has been described, with the observation that the clinical picture may not correlate with the X-ray findings. The value of routine chest films is again made evident.

Varicella in an adult is potentially a more serious illness than in children. Pregnancy increases the risk. A plea is made for increased awareness of this complication and for early, vigorous management.

Summario in Interlingua

Primari pneumonia a varicella ha solo recentemente essite recognoscite como un serie e a vices mortal complication de varicella in adultos. Le presente reporto adde 13 casos al litteratura e sublinea le facto que le incidentia de pneumonia in adultos con varicella es multo plus alte que lo que esseva credite in le passato.

Trenta-octo adultos con varicella esseva admittite al Hospital Meadowbrook (Hempstead, New York) durante le periodo ab januario 1953 usque al fin de julio 1960. Dece-tres de iste patientes exhibiva signos clinic o roentgenographic (o ambes) de pneumonia a varicella. Le etates in iste gruppo variava inter 20 e 47 annos. Le apparentia radiographic non esseva correlationate con le tableau clinic in le tres casos in que le constatationes roentgenographic esseva typic durante que pauc symptomas clinic esseva presente. Quatro casos non haberea essite diagnosticate correctemente si nulle radiographias haberea essite facite. Dece-duo del adultos con varicella non esseva radiographate. Isto pare indicar que le ver incidentia de pneumonia como complication de varicella in adultos es probabilemente ancora plus alte.

Pneumonia a varicella in le patiente adulte pote exhibir un si micre numero de symptomas que le diagnose deveni evidente solmente a base del radiographia. Del altere latere, illo pote devenir, intra 24 a 48 horas un processo fulminante con termination mortal. Il existe nulle criterios que permitte predicer qual patiente va disveloppar pneumonia o in qual casos le pneumonitis va esser sever.

Le tractamento es supportative. Septe del patientes in le presente serie requireva oxygeno e liquido intravenose. Antibioticos es indicate quando infection secundari superveni. Le uso de steroides deberea esser reservate pro casos complicate per choc o insufficientia adrenal. Nulle morte occurreva in le presente serie.

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CASE REPORTS

Pure Nephrosis in an Adult Patient

Serial Observations of Blood Volume, Serum Electrolytes, and Renal Function

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A YOUNG WOMAN with the characteristic features of pure nephrosis was successfully treated with steroids at H. C. Moffitt Hospital. The clinical course and results of serial determinations of blood volume, creatinine clearance, serum proteins, and electrolytes before, during, and after treatment are described in this report.

This case is of particular interest (1) because of an episode of shock attributable in part to a diminished blood volume and in part to the administration of medication with antihypertensive properties; (2) because of the dramatic response to adrenal steroid therapy, accompanied by rapid disappearance of proteinuria and spectacular recovery of serum proteins and blood volume; (3) because of the interesting electrolyte changes which occurred; (4) because of maintenance of a glomerular filtration rate which remained within normal limits despite hypovolemia.

CASE REPORT

A 35-year-old housewife was admitted to another hospital on January 24, 1958, because of mild abdominal pain, puffiness about the face and extremities, and malaise of one month's duration. She was edematous at the time, but did not appear acutely ill; blood pressure was normal. Significant laboratory findings were hypoalbuminemia; hematocrit, 43%; proteinuria; creatinine clearance of 123 ml/min; and antistreptolysin titer of 12 Todd units. She had been in good health previously and had no history of renal disease. She was referred to H. C. Moffitt Hospital for evaluation and treatment on February 9 and again on September 19. Blood volume changes during the period of observation are summarized in Table 1. Clinical and laboratory data are graphed in Figure 1 and the serum electrophoretic patterns in Figure 2.

FIRST HOSPITALIZATION

At the time of admission the patient was a well-developed, alert young woman in no distress. Blood pressure (supine position) was 100/70 mm Hg; pulse, 106/min. Respiration and temperature were normal. Periorbital puffiness and 2+ sacral edema were present, but she had no ascites or peripheral edema. The costovertebral angles were not tender to palpation. No other physical abnormalities were found.

Laboratory tests gave the following results: hematocrit, 55%; hemoglobin, 18 g/100 ml; white blood cells, 6,800/mm^3; differential count and platelets, normal. Specific gravity of the urine was 1.005, the pH 7; the sediment contained five red blood cells per high power field and an occasional hyaline cast, but no lipid casts or oval fat bodies. Urinary protein was 4+ qualitatively and 7.7 g/24 hr quantitatively. Total serum protein was 4.4 g, albumin 0.8 g, and globulin 3.6 g/100 ml. Total blood cholesterol was 456 mg/100 ml. Serum sodium was 135, chloride, 103, potassium, 6, and carbon dioxide 30 mEq/liter. Corrected creatinine clearance was 89 ml/min and serum creatinine 0.8 mg/100 ml. A throat culture was negative for beta hemolytic streptococci. An electrocardiogram was normal. Total blood volume (Table 1), determined by the Cr^{51}-labeled red cell technique (1), was 2.43 liters, or 71% of the patient's normal total blood

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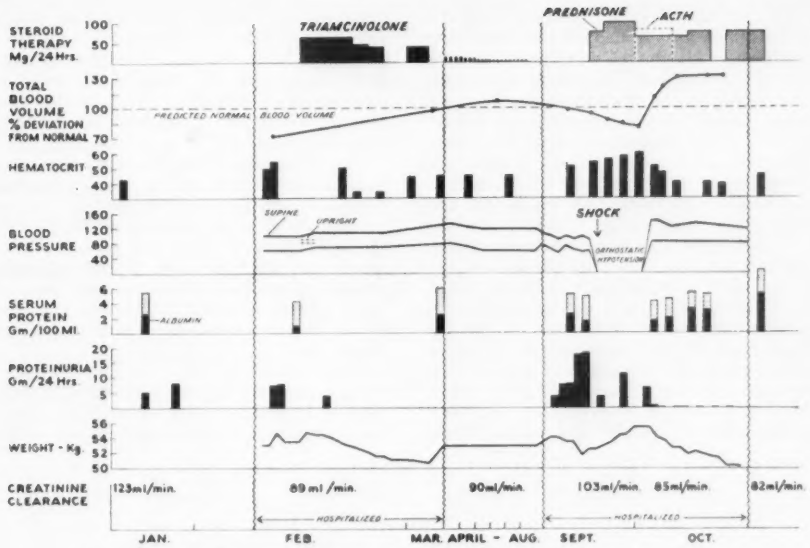


FIGURE 1. Clinical course of patient during ten-month period of observation.

volume predicted on the basis of her height and pre-edema weight, according to the regression equations of Wennesland, Brown, Hopper, Hodges, Guttentag, Scott, Tucker, and Bradley (2).

Steroid therapy, consisting of 64 mg of triamcinolone * per 24 hr, was initiated on February 13. At this time the urinary protein was 10.8 g/24 hr and serum electrophoresis showed a marked reduction in the albumin peak (Figure 2). Six days later diuresis began, and for the first time the urine was free of protein. The patient's edema decreased rapidly as diuresis continued. The only complication during steroid therapy was transient mild swelling and aching of the left knee. On March 3, the eighteenth day of treatment, total serum protein measured 6.2 and albumin 3.8 g/100 ml. Total blood volume at this time was 3.09 liters, or 90% of the predicted normal volume. Daily urinalysis showed no proteinuria or other abnormalities. The patient was discharged on March 5 with instructions to take 40 mg of triamcinolone daily for three successive days each week.

The patient was seen as an outpatient from March to September. During this time the blood pressure fluctuated between 115/75 and 135/80 mm Hg. Results of renal function tests were normal; proteinuria and edema were absent. The dose of triamcinolone was gradually reduced to 12 mg daily for three successive days each week. In August the patient stopped taking the steroid without consulting her physician. On September 8 she showed a trace of pedal edema. On September 13 urinary protein was 4+. The patient was readmitted to the hospital on September 19 for additional treatment with steroids.

* Supplied as Kenacort® by E. R. Squibb & Sons.

SECOND HOSPITALIZATION

The patient was slightly edematous at the time of admission. Blood pressure was 150/70 mm Hg, the pulse rate, 80/min. Respirations and temperature were normal. Results of routine laboratory studies were as follows: hematocrit, 51%; hemoglobin, 17.2 g/100 ml; red blood cells, 5.20 million/mm^3; white blood cell count and differential, normal; platelets, normal. The specific gravity of the urine was 1.015, the pH, 8; the sediment contained a rare red blood cell and 0 to 1 hyaline cast per high power field; no granular, fatty, or cellular casts were seen. Urinary protein was 4+ qualitatively and 3.1 g/24 hr quantitatively. Total serum protein was 5.3 g, albumin 2.5 g, and globulin 2.8 g/100 ml. Total blood cholesterol was 332 mg/100 ml. Serum creatinine was 0.8 mg/100 ml, the corrected creatinine clearance 102 ml/min. In additional tests on September 22 (Table 2), serum sodium was 142 and potassium 5 mEq/liter. Examination of peripheral blood for lupus erythematosus cells was negative. Total blood volume, determined by the Cr^{51} technique, was 3.26 liters, or 95% of the predicted volume (Table 1). X rays of the chest showed no evidence of cardiovascular or pulmonary disease.

The patient developed an upper respiratory tract infection shortly after admission. For this reason, steroid therapy was not initiated at once; sodium intake, however, was immediately restricted to 250 mg/ day. During the next seven days urinary protein rose progressively from 3.1 to 17.6 g/24 hr,

serum albumin concentration decreased from 2.5 to 1.3 g/100 ml, and the hematocrit rose from 51% to 54%. During this period total blood volume fell from 3.26 to 3.04 liters. Treatment with prednisone was begun on the seventh hospital day; the dose ranged from 50 to 100 mg daily. The following day the patient complained of nausea, weakness, vague aches in the extremities and abdomen, and orthostatic discomfort, which she ascribed to oncoming menses. To relieve her discomfort, she was given 25 mg of promazine hydrochloride, injected subcutaneosuly, and 10 mg of codeine orally. Approximately one-half hour later the patient was cyanotic and in a profound state of shock. Blood pressure and pulse rate could not be determined. Immediate intravenous administration of 150 mg of hydrocortisone, 25 g of albumin, and 10 mg of metaraminol bitartrate resulted in a return to a normotensive state during the next hour. After the episode of shock, the blood pressure was 100/80 mm Hg when the patient was supine; when standing, the pressure could not be determined and she felt faint. By October 1 (sixth day after shock) the hematocrit had risen progressively from 54% to a high of 60%. Total blood volume at this time measured 2.65 liters (77% of the predicted normal volume, 610 ml less than the volume at the time of admission).

The patient was given oral supplements of potassium (24 to 36 mEq daily) from the eleventh to the nineteenth hospital day. ACTH (80 units/24 hr) was added to her regimen on the twelfth day. Clorothiazide, 1 g daily, was given on the fourteenth and fifteenth days. By the fifteenth day urinary protein had dropped to trace amounts and blood volume measured 1% greater than the predicted normal. Orthostatic hypotension was no longer present.

Serum sodium at this time was 114 mEq/liter. Because electrolyte determinations had shown no significant sodium deficits during the period of hospitalization and the patient appeared clinically

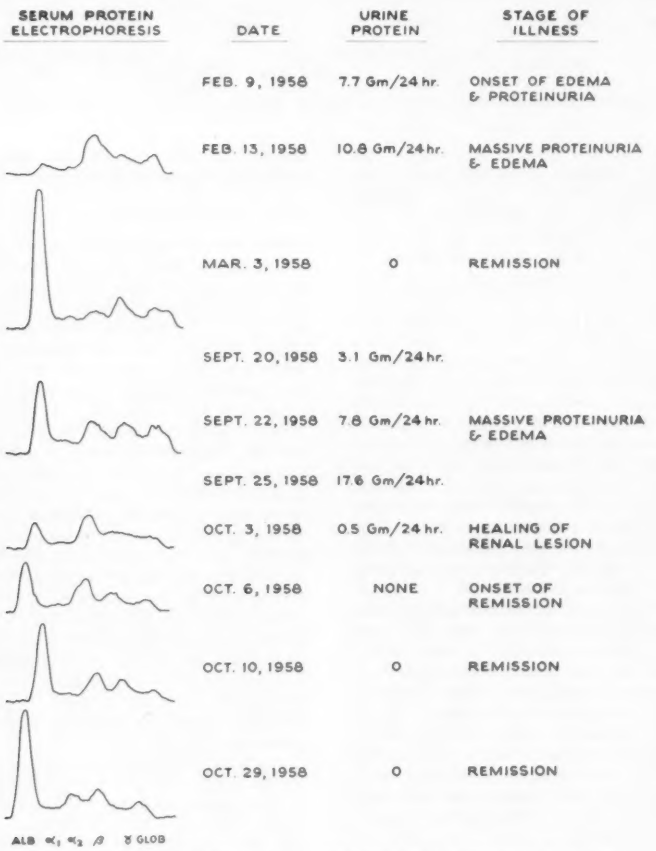


FIGURE 2. Electrophoretic patterns, showing rapid alterations in serum protein levels during the course of illness.

TABLE 1. Blood Volume Changes During Nephrotic Episodes and Remissions

Clinical Status and Date	Measured Blood Volume* liters			Percentage of Predicted Total Volume‡	Hct. %	Hemoglobin g/100 ml
	Total	Red Cell	Plasma†			
First hospitalization: 2/9/58						
Nephrotic state						
2/11	2.43	1.34	1.09	71	55	18
Remission						
3/3	3.09	1.55	1.55	90	50	—
Outpatient: 7/7/58	3.44	1.55	1.89	100	45	—
Second hospitalization: 9/19/58						
Exacerbation of nephrotic state						
9/22	3.26	1.66	1.60	95	51	17.2
9/25	3.04	—	(1.41)	88	54	18.3
Shock: 9/26						
Orthostatic hypotension						
9/27	2.89	—	(1.28)	84	56	19.3
9/29	2.78	—	(1.19)	80	58	19.8
10/1	2.65	—	(1.09)	77	60	20.8
Remission						
10/3	3.47	1.56	1.91	101	52	16.6
10/4	3.74	—	(2.18)	108	47	16
10/6	4.33	—	(2.77)	126	42	13.8
10/10	4.33	—	(2.77)	126	42	—

* Cr^{51}-labeled red cell technique (1).

† Predicted total blood volume estimated on basis of patient's height (161 cm) and pre-edema weight (52 kg) was 3.44 liters (100%).

‡ Figures in parentheses = changes in plasma volume, PV_2/PV_1, estimated from the formula $Hb_1/Hb_2 \times 1\text{-}Hct_2/2\text{-}Hct_1 \times 100$.

well, salt restriction and potassium supplementation were continued during the period of hyponatremia. By the twentieth day (October 8) serum sodium had returned to a level of 140 mEq/liter. Diuresis and stabilization of blood pressure resulted in rapid clinical improvement. On October 10, total blood volume was 4.33 liters, or 26% greater than the predicted normal. The patient was dismissed from the hospital on October 14, 1958.

DISCUSSION

DIAGNOSIS

Although the diagnosis was not established by renal biopsy, this case had the characteristic features of a "pure" nephrotic state. A pure nephrotic state, as we define it, is characterized clinically by salt and water retention (edema), massive proteinuria, hypoalbuminemia, and hyperlipidemia. Renal function tends to be normal and may even be supranormal, no hypertension is present, and no or only a few red blood cells are found in the urine (4). On examination by light microscopy, the kidney may appear normal, but electron microscopy

TABLE 2. Serum and Urine Electrolyte Levels During Second Hospitalization

Date	Body Weight, Kg.	Serum Na mEq/Liter	Serum K mEq/Liter	Urine Na mEq/24 hr	Urine K mEq/24 hr	Serum Water* %
9/22	53.5	142	5	35	47	—
9/23	51.7	—	—	24	67	—
9/24	52.5	—	—	8	78	—
9/29	54.6	—	—	0.8	48.6	—
10/3	54	114	3.9	—	—	93
10/4	53.5	119	—	19	173	—
10/8	51.5	140	5.5	—	—	—
10/10	50.5	140	—	—	—	—

* Method of Albrink et al. (3).

always shows glomerular changes involving the epithelial cells and their foot processes (4, 5).

This patient had edema, hypoalbuminemia, hypercholesteremia, and massive proteinuria without notable hematuria or abnormal urinary casts, and she was normotensive and had normal renal function, all of which fit the clinical description of a pure nephrotic state. Treatment with corticosteroids resulted in rapid disappearance of proteinuria. Although the etiologic diagnosis of nephrotic states in adults without the use of renal biopsy is subject to error (6), we think the response to therapy further supports the diagnosis of pure nephrosis. In our experience, this is the type of nephrotic state which responds best to adrenal steroid therapy.

RESPONSE TO THERAPY

On occasion we have seen an extremely rapid improvement of the nephrotic state following adrenal corticoid therapy, as evidenced by rapid disappearance of proteinuria and increase in the serum albumin, but never in an adult patient have we seen as dramatic a response as occurred in this case. As shown in Figure 1, in the first period of hospitalization 24-hour urinary excretion of protein decreased from 10.8 to 0 grams during the first six days of steroid therapy, after which the urine remained protein-free. In the second period of hospitalization, the 24-hour urinary protein output had decreased from 17.6 to 0 grams by the tenth day of therapy, after which the urine again remained protein-free. In both instances the decrease was accompanied by rapid changes in serum proteins (Figure 2). With cessation of proteinuria and restitution of protein stores, plasma volume was rapidly reconstituted (Table 1).*

*Subsequently, on July 27, 1959, while the patient was on an interrupted treatment schedule (corticoids, 20 milligrams daily for three consecutive days per week, followed by a rest period of four days), she relapsed into a nephrotic state. She again responded rapidly to administration of prednisone, 100 mg/day. The patient is now taking 20 milligrams of prednisone daily three successive days of each week, and up to the time of this report has had no proteinuria. She is being seen at monthly intervals. Blood pressure and renal function continue to be normal. The patient has been taught to test her urine for protein, which she does once a week. We plan to withdraw treatment gradually after her urine has been free of protein for one year.

HYPOVOLEMIA AND SHOCK

It is well known that the serum albumin, by the colloid osmotic pressure it exerts, is an important factor in maintaining circulatory plasma volume (7–9). In our experience, approximately 50% of adult nephrotics have a reduced blood volume, largely attributable to a decrease in plasma volume or inability to compensate for anemia by an appropriate increase in plasma volume. The other 50% appear able to make adequate compensation; in 40% blood volume is normal, while in 10% it is increased (10).

In our patient, the rapid and progressive increase in proteinuria during the second period of hospitalization was accompanied by an equally rapid diminution of both serum albumin and plasma volume (Table 1), making the patient susceptible to shock. For five days after the episode of shock precipitated by subcutaneously administered promazine hydrochloride, the patient's plasma volume decreased progressively as her protein stores became depleted, and extreme orthostatic hypotension was present. The fact that no further shock occurred at this time may be attributed to bed rest, avoidance of manipulative procedures, and treatment with steroids. Following cessation of proteinuria, both serum albumin and plasma volume returned to normal.

While intravenous administration of plasma or albumin will cause restitution of plasma volume in hypovolemic nephrotic patients, the effect is temporary. In less than 24 hours, the plasma volume is usually again depleted, mainly because of augmentation of the heavy proteinuria these patients always have. For effective control of the hypovolemia of nephrosis, it is necessary to arrest the proteinuria, which can sometimes be accomplished by adrenal corticoid therapy.

RENAL FUNCTION DURING HYPOVOLEMIA

It is well known that in the pure nephrotic state renal function may be normal or supernormal (11–13). In this patient, creatinine clearance was notably good despite a critical reduction in blood volume. At the time of her first admission to the hospital, when blood volume was 71% of the predicted value, creatinine clearance was 80 ml per minute. The day after the episode of shock during the second hospitalization, it was 103 ml per minute. While it

appears contradictory that glomerular function can be maintained in nephrotic patients with reduced blood volume, we have made this observation in other patients (both adults and children) with nephrotic states.

DANGER OF HYPOTENSIVE DRUGS IN NEPHROSIS

This case illustrates the danger of using drugs likely to reduce blood pressure in nephrosis. Twenty-five milligrams of promazine hydrochloride, given subcutaneously to this patient while she was at strict bed rest, resulted in profound shock within a half-hour. Promazine is known to produce orthostatic hypotension, but only when large doses are administered intramuscularly or intravenously (14).

Another example of the danger of hypotensive drugs in nephrotic patients is the case of a 39-year-old woman with a nephrotic state who was given 0.4 milligram of nitroglycerin sublingually for vague precordial and epigastric pain. Her blood pressure (recumbent) dropped to 60/0 mm Hg, and she lapsed into a shock-like state from which she fortunately recovered after administration of hypertonic glucose solution and whole blood.

Hypovolemic nephrotic patients are equally sensitive to surgical procedures. We have reported death due to shock following a renal biopsy, accompanied by the loss of an amount of blood usually well tolerated (15). "Spontaneous" hypovolemic shock leading to death has been observed in two nephrotic patients, one of whom was described in a previous communication (9). In both patients, renal insufficiency was minimal and autopsy did not reveal the cause of death.

ELECTROLYTE PICTURE (TABLE 2)

At the time of the present patient's second admission to the hospital, the serum sodium concentration was 142 mEq/liter. During the first 15 days her diet contained 20 milliequivalents of sodium and approximately 80 milliequivalents of potassium daily. Potassium supplementation was begun on the eleventh hospital day. Chlorothiazide, one gram daily, was given on the fourteenth and fifteenth days. By the fifteenth day the serum sodium had dropped to 114 mEq/liter. Because electrolyte determinations had shown no significant sodium loss and the patient was not acutely ill, sodium restriction and potassium supplements were continued. Within the next five days, the serum sodium level returned to normal. Coincident with the rapid, complete resolution of the nephrotic state and loss of 2.5 kilograms in weight, serum sodium rose to 140 mEq/liter.

The fact that the patient gained only one-half kilogram in weight and that her sodium intake was estimated to exceed output during the first 15 days of hospitalization indicates that the hyponatremia probably was not caused by salt depletion or excessive retention of water. This impression is supported by the return to normal of the serum sodium concentration within five days while dietary restriction of salt and potassium supplementation were continued (Table 2). In analyzing the probable pathogenesis of hyponatremia in the present case, the studies of Edelman, Leibman, O'Meara, and Birkenfeld (16) appear particularly germane. First, they minimized the role of compartmental shifts of sodium in the development of hyponatremia, a mechanism which might have been postulated in our case; and second, they found that the sodium concentration was a function of exchangeable body sodium and potassium and total body water. Although their subjects included only a few nephrotics, their conclusions are probably valid when applied to the hyponatremia of nephrosis. On this basis, we have postulated that the hyponatremia in our patient could be attributed primarily to loss of potassium, which resulted in a fall in intracellular osmolarity, leading to a shift of water from the intracellular to the extracellular compartment and a consequent decrease in extracellular sodium concentration. With the restoration of cellular potassium, extracellular water was redistributed to the intracellular compartment, resulting in restoration of extracellular sodium concentration to normal. Luetscher (17), in a study on electrolyte equilibrium in the nephrotic syndrome, found that hyponatremia was not uncommon in nephrotic patients. He demonstrated that parenteral administration of hypertonic saline was rarely helpful in raising the serum sodium concentration, whereas administration of human serum albumin without additional sodium would restore the serum sodium level to normal. In one of his patients, metabolic studies showed a positive potassium balance during the period of correction of

serum sodium concentration with salt-poor albumin.

Regardless of the mechanism involved, it was remarkable that our patient developed severe hyponatremia over a six-day period, that the hyponatremia was not associated with symptoms of sodium depletion or water intoxication, and that restoration to a eunatremic state occurred in an equally short period despite continued dietary salt restriction and after only a slight loss in body weight.

It is concluded that, with nephrotic edema, diminution of serum sodium concentration may be well tolerated and does not necessarily indicate the need for sodium. It is important, however, to ensure an adequate source of potassium.

Summary

A young woman with the characteristic features of pure nephrosis was hospitalized twice in ten months because of edema and proteinuria. Serial determinations of blood volume, serum electrolytes, and renal function were carried out during both periods of hospitalization. During an exacerbation of the disease, the patient showed a rapid, progressive increase in proteinuria, a decrease in serum albumin, and a reduction in plasma volume. Despite the decrease in circulatory volume, renal function was maintained. While the patient was hypovolemic, shock was precipitated by subcutaneous injection of a small amount of promazine hydrochloride. Other accidents in hypovolemic nephrotic patients are cited.

Observation of a diminished serum sodium concentration during the course of heavy proteinuria was most adequately explained by loss of cellular potassium. This loss caused a diminution in cellular osmolarity, with consequent shift of water into the extracellular space. Restitution occurred during sodium restriction and potassium supplementation and reflected the movement of potassium and water back into cells.

This case illustrates the extremely rapid deterioration that can occur in patients with an active nephrotic lesion and their equally rapid response to steroid therapy, as evidenced by prompt disappearance of proteinuria and return of serum protein, cholesterol, and electrolyte levels to normal. It also dramatically illustrates the dangers of administering drugs that might have a hypotensive effect in the presence of hypovolemia.

Summario in Interlingua

Un juvene femina con le characteristicas typic de pur nephrosis esseva hospitalisate duo vices in dece menses a causa de edema e proteinuria. Determinationes serial del volumine de sanguine, del electrolytos del sero, e del function renal esseva executate durante ambe periodos de hospitalisation. Al occasion del prime hospitalisation, therapia a steroides resultava in un prompte remission del stato nephrotic, lo que esseva evidentiate per le disparition del proteinuria. Le patiente esseva congedate con le instruction de continuar prender doses de mantenentia del steroide. Approximativemente sex menses plus tarde illa cessava prender le medication. Edema e proteinuria recurreva brevemente postea, e illa esseva hospitalisate de novo pro evalutation e tractamento.

Therapia a steroides non esseva comenciate ante le septime die al hospital, sed le ingestion dietari de natrium esseva restringite immediatemente. In le curso del sequente septe dies, le proteinuria se intensificava marcatemente. In plus, le concentration del albumina seral declinava, e le volumine de sanguine total esseva reducite a 88% del estimate volumine normal. In despecto del reducite volumine circulatori, le function renal se manteneva. Tamen, iste grado de hypovolemia pareva predisponer le patiente a choc, proque le administration a iste tempore de un micre quantitate de hydrochloruro de promazina esseva sequite intra un medie hora per un sever episodio hypotensive. Post appropriate mesuras therapeutic, le tension de sanguine retornava al norma. Le occurrentia de hyponatriemia post le episodio de choc esseva attribuite a carentia de kalium, ben que supplementos de kalium habeva essite addite al dieta le dece-prime die del sojorno al hospital. Con le continuation del therapia a steroide, un dieta a basse contento de sal, e le ingestion de supplementos de kalium, le proteinuria dispareva, e le natrium del sero e le volumine total de sanguine retornava a nivellos normal.

Iste caso illustra le extrememente rapide deterioration que pote occurrer in patientes con active lesion nephrotic e lor equalmente rapide responsa a therapia a steroides, manifeste in le prompte disparition del proteinuria e le retorno a nivellos normal del proteina, cholesterol, e electrolytos del sero. Le caso etiam signala le periculo que inhere in le administration de drogas potentialmente hypotensive in le presentia de hypovolemia.

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Hypogonadotrophic Hypogonadism Simulating Turner's Syndrome

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The clinical manifestations of panhypopituitarism secondary to destruction of the adenohypophysis are well known. After its original description by Simmonds (1) in 1914, panhypopituitarism was the subject of many case reports and reviews (2–5). Marked insufficiency of the target glands and profound cachexia were stressed. Sheehan and Murdoch (6, 7) first emphasized that most patients with pituitary insufficiency are not cachetic and that there is a wide clinical spectrum of pituitary dysfunction. Hypopituitarism may vary from

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FIGURE 1. Showing short, webbed neck, shield chest, widely spaced nipples, cubitus valgus, lack of secondary sex characteristics including pubic hair, and sexual infantilism.

mild involvement of one or more of the target glands to severe insufficiency of all three principal organs (6–8). The clinical course may range from a chronic one, with slowly progressive involvement of the thyroid, gonads, and adrenal cortex over many years, to an acute course, with death in days or weeks (6–9). Impairment of function corresponds more or less to the degree of pituitary destruction, regardless of etiology (10). In recent years, there has been increasing awareness of the syndromes of incomplete pituitary failure (11, 12).

In 1935, Albright and Halsted (13) presented two cases of hypogonadism secondary to failure of secretion of pituitary gonadotrophin with no evidence of other pituitary insufficiency. Similar cases were reported by Fraser, Forbes, Albright, Sulkowitch, and Reifenstein (14), by Klinefelter, Albright, and Griswold (15), and by Wilkins and Fleischmann (16). Since then, there has been increasing recognition and acceptance of the clinical entity of selective pituitary failure (9, 11). The most common type of the latter group is hypogonadotrophic hypogonadism, characterized by eunuchoidism and hypogonadism (9, 11, 17). Additional congenital anomalies have not been previously reported in association with this entity.

In 1938, Turner (18) described a syndrome in phenotypic females of congenital anomalies and hypogonadism manifested by sexual infantilism, short stature, webbed neck, and cubitus valgus. It was subsequently demonstrated that the sexual infantilism was due to ovarian agenesis (12, 19–21). Patients with ovarian agenesis all have in common the presence of rudimentary ovaries, incapable of normal ovarian function, resulting in primary ovarian failure and hypogonadism (10, 19–24). A distinguishing characteristic of Turner's syndrome is a consistent elevation in the urinary gonadotrophin titer (10, 20–22, 25). Although occasional cases with normal or low urinary gonadotrophins have been described (24, 26–29), there are no well documented adult cases in the literature of Turner's syndrome with absent urinary gonadotrophins. Thus, in both Turner's syndrome and in hypogonadotrophic hypogonadism the presenting complaints may relate to hypogonadism, but definite differences usually exist, notably the absence of congenital anomalies and urinary gonadotrophins in the latter entity.

It is the purpose of this report to describe a case of hypogonadotrophic hypogonadism simulating Turner's syndrome. To our knowledge, this has not been peviously reported.

CASE REPORT

A 28-year-old Puerto Rican female was admitted for study of primary amenorrhea. She had never had a menstrual flow, had not noted breast development or growth of pubic or axillary hair, and had never been pregnant. There was no history of pelvic inflammatory disease, irradiation to the pelves, vaginal discharge, or dyspareunia. She claimed to have a normal libido, and had been married nine years.

Review of Symptoms: Two years prior to admission the patient developed a right hemiparesis with

dysarthria that gradually cleared with little residuum. At that time she had hypertension. One year prior to admission she developed angina on exertion, and some dyspnea on exertion about six months later. She recalled frequent episodes of tonsillitis as a child, and an episode of transient facial and ankle edema. There was no other significant history of neurological, cardiovascular, or urinary difficulties.

Family History: The patient's father died of a cerebrovascular accident and her mother is alive, but has "diabetes and heart failure." Five living sisters have normal menses; four are married and have children. Four brothers are alive and well.

Physical Examination: The patient was a well nourished female, height 62 inches. She had a short, webbed neck, shield chest, widely spaced small nipples, cubitus valgus, abnormal lateral extension of the fifth finger of each hand, and lack of secondary sex characteristics, including breast tissue and pubic and axillary hair (Figure 1). She had sexual infantilism, with infantile but female external genitalia, narrow pubic arch and vaginal canal, atrophic vaginal mucosa, and infantile cervix and uterus. The adnexae were not felt. Her skin was warm and dry, with normal texture and hair. The fundi showed grade 2 Keith-Wagener changes. The heart was slightly enlarged to the left and no murmurs were heard. Femoral pulsations were normal. There was some residual weakness and hyperreflexia of the right arm and leg. The rest of the examination was within normal limits.

Laboratory Data: Blood pressure was 140/100 mm Hg; pulse, 80/minute; respirations, 12/minute; temperature, 99 F. Hemoglobin was 11 mg/100 ml; white blood count, 6,100/mm³, with a



FIGURE 2. Normal intravenous pyelogram, also showing the retardation of bone development, with delayed epiphyseal closure.



FIGURE 3. X ray of hands showing delayed epiphyseal closure and abnormal lateral extension of fifth finger.

normal differential; platelets, 190,000/mm³; erythrocyte sedimentation rate, 30 mm the first hour. Urine specific gravity ranged from 1.010 to 1.024 with a trace of albumin and 15 to 20 white blood cells per high power field. Urine culture showed *Escherichia coli*. The Esbach determination was 1 g/24 hours. Phenolsulphonphthalein excretion was 20% in 15 minutes and 65% in two hours. Blood urea nitrogen ranged from 25 to 40 mg/100 ml; serum creatinine from 1.1 to 1.7 mg/100 ml. Fasting blood sugar was 68 mg/100 ml; serum uric acid, 7.5 mg/100 ml; serum albumin, 3.9 mg/100 ml; serum globulin, 4.3 mg/100 ml; serum cholesterol, 273 mg/100 ml; serum phospholipids, 270 mg/100 ml; total serum lipids, 1,035 mg/100 ml. Serum electrolytes, calcium, phosphorus, and alkaline phosphatase were within normal limits. Three lupus preparations were negative. Serum electrophoresis showed a slight elevation of the gamma globulin.

Urinary neutral 17-ketosteroids were 6.4 mg/24 hours; urinary 17-hydroxycorticosteroids, 6 mg/24 hours, and urinary 24-hour gonadotrophins * were negative at a titer of 2.5 mouse units on three occasions. Protein bound iodine was 5.1 g/100 ml, and the 24-hour radioactive iodine uptake was 35%. Vaginal smear showed severe estrogen deficiency with chromatin positive cells; a skin biopsy similarly revealed a chromatin positive pattern, as seen in females. Vanillyl mandelic acid test for pheochromocytoma was negative.

A chest X ray was normal. An intravenous pyelogram with three, five, ten, and 20 minute films showed prompt bilateral excretion with normal calyces. The kidneys were slightly smaller than normal. Bone survey showed retarded bone development, with the epiphyses not fused, and a bone age of 17 years (Figures 2 and 3). The bones were somewhat gracile and minimally lengthened, with normal mineralization. A left carotid arteriogram and pneumoencephalogram were normal. Cerebrospinal fluid was normal, as was a neurological skull series.

An electrocardiogram showed an old anteroseptal wall myocardial infarction. The venous pressure and circulation time were normal.

This patient apparently had multiple disorders, including hyperlipemia, coronary artery disease, cerebrovascular disease, hypertension, and renal disease or cerebrovascular anomaly.

DISCUSSION

The adenohypophysis secretes at least seven hormones; growth hormone, ACTH, thyroid

* Gonadotrophin activity of urine assayed by modification of the method of Klinefelter et al. (15) using the kaolin adsorption method of Bradbury et al. (30). Normal range, greater than 6.6 to less than 53 mouse units per 24 hours.

stimulating hormone, lactogenic hormone, melanocyte stimulating hormone, and the two gonadotrophic hormones (11). Studies in animals suggest that each pituitary hormone is derived from a specific cell type (31). It may now be regarded as established that selective pituitary failure occurs in animals and in man (9, 11, 12). This may be detected only by hormonal assay, for often in life there is no obvious lesion in the pituitary, and clinically the disorder may be indistinguishable from primary failure of the target gland (11, 17). The most frequent type of selective failure is a diminution or absence of secretion of gonadotrophins (9, 11).

Deficiency or total absence of gonadotrophin secretion can be caused by a developmental defect of the adenohypophysis. Hypogonadism and eunuchoidism result, in both males and females, since the onset is prior to puberty (9, 11, 17). In hypogonadotrophic hypogonadism, because of failure of normal gonadal maturation and sex hormone secretion, in both males and females, there is a failure to mature at puberty, a lack of development of normal secondary sex characteristics, and a characteristic tall, eunuchoid habitus. In the male, there are infantile external genitalia, absent or scanty pubic hair, and absence of normal masculinity. Testicular biopsy reveals tissue resembling the testes of a prepubertal male. The tubules are infantile in development, with lumenless cords, no differentiation of Sertoli's cells, and with primitive and inactive germ cells. There are few Leydig's cells or they are absent. Impotence and lack of libido are characteristic (17). In the female, there are primary amenorrhea, infantile external genitalia, and infantile uterus and ovaries; breast tissue is lacking, pubic hair is scanty or lacking, and normal female habitus is lacking. Ovarian biopsy shows essentially normal prepubertal ovarian tissue. Follicles are immature and fewer than normal (9, 11, 22, 32). In both males and females, the urinary gonadotrophins are absent, the levels of the urinary neutral 17-ketosteroids are normal, the nuclear sex chromatin pattern is normal, the bone age is retarded, and there may be osteoporosis. Primary hypogonadism can be distinguished by an elevated urinary gonadotrophin titer (9, 11, 17, 22).

Since Turner's original report, there have been numerous descriptions and reviews of the syndrome in the literature (18–21, 23–25). The condition has been variously described as Turner's syndrome, Turner-Varney's syndrome, Albright's syndrome, ovarian agenesis, rudimentary ovary syndrome, and ovarian aplasia (18–21, 23, 25). Since the discovery that the hypogonadism in Turner's syndrome resulted from ovarian agenesis, further investigation through the years has broadened the clinical concept of ovarian agenesis. Patients with this defect in ovarian development all have hypogonadism. However, these patients may be short in stature and may have associated congenital anomalies, or may be normal in height and may have no anomalies (10, 22–24). The combination of ovarian agenesis with hypogonadism and the somatic anomalies described by Turner is referred to as Turner's syndrome. Thus this syndrome is a subdivision of a larger group of patients with primary ovarian failure due to ovarian agenesis (22, 24). More recent investigations of ovarian agenesis have included the application of sex chromatin studies and chromosome counting (33). In approximately 80% of patients with ovarian agenesis, a chromatin negative nuclear sex pattern has been found (10, 22, 33a, c). This is the usual pattern in the normal male (22, 33). The theory has been proposed that many patients with ovarian agenesis represent genetic males whose testes never developed or functioned in utero, with resultant female phenotype (10, 22, 24, 33). It has been suggested that these patients be considered to have gonadal dysgenesis rather than ovarian agenesis (24). However, chromosome counting in these patients with chromatin negative nuclear sex patterns has revealed that they have only 45 chromosomes, with no Y chromosome, and an XO pattern (33a).

Turner's syndrome can be considered under three salient features: gonadal, skeletal, and other somatic anomalies (23).

These patients have primary ovarian deficiency. Due to a congenital defect the ovaries fail to develop beyond the primitive genital ridge stage, and epithelial proliferation and primordial germ cells are characteristically absent. Ovarian stroma is usually present. Although pituitary gonadotrophin secretion may be normal or elevated, the ovaries are incapable of response. As a result, patients with this dis-

order fail to mature at puberty and maintain infantile internal and external genitalia. There are primary amenorrhea and failure of development of the other secondary sex characteristics, with resultant prepubertal breasts and pinpoint nipples. Pubic hair is usually present, but may be decreased. Generalized osteoporosis is frequent. In common with other types of primary hypogonadism, adult patients have an elevated urinary gonadotrophin excretion and low estrogen excretion. The urinary neutral 17-ketosteroid values are reduced. Estrogen therapy results in some development of secondary sex characteristics (10, 18–25).

The second aspect of Turner's syndrome is concerned with the skeletal changes. There is a characteristic habitus, with short stature (usually 48 to 56 inches), thick-set stocky build with good muscular development, a shield-like chest (the thorax being prominent anteriorly, broader than normal, with widely spaced nipples and increased anteroposterior diameter), and arm span several inches greater than height. Cubitus valgus (an increased carrying angle between the humerus and radius) is usually present. Other skeletal abnormalities may include pes cavus, syndactyly, osteogenesis imperfecta, anomalous positions of the toe or finger, spina bifida occulta, abnormal rib development, fusion of cervical vertebrae, and hammer toe (10, 18–25).

The third feature consists of congenital anomalies, some of which have been listed under the skeletal abnormalities. The most common are webbing of the neck and cubitus valgus. Other anomalies include coarctation of the aorta, deafness, mental deficiency, ptosis, squint, cataracts, tubular vision, exophthalamus, lack of retinal pigment, and independent hypertension. The shortness of stature is also considered to be an anomaly (10, 18–25).

When the complete syndrome is present, with multiple skeletal and congenital anomalies, the diagnosis can be suspected clinically. It may be confirmed by the presence of elevated urinary gonadotrophin titers and vestigial ovaries on laparotomy. In 80% of the cases, a male sex chromatin pattern is found. The presence of a male sex chromatin pattern and elevated gonadotrophins can be considered as diagnostic even in the absence of the surgical visualization and histological study of the ovaries (23, 24a).

The case presented by us is one of hypogonadotrophic hypogonadism. The patient had a normal serum protein bound iodine, normal 24-hour I^{131} uptake, and normal urinary excretion of neutral 17-ketosteroids and 17-hydroxycorticosteroids. There was, thus, no clinical or laboratory evidence of thyroidal or adrenocortical dysfunction, and no evidence of pituitary dysfunction other than absent urinary gonadotrophins. She presented with primary amenorrhea, sexual infantilism, lack of other secondary sex characteristics, and gracile bones with a markedly retarded bone age. She was lacking in pubic and axillary hair, and had a female sex chromatin pattern. All of these clinical and laboratory findings are characteristic of hypogonadotrophic hypogonadism.

The unusual aspect of this case is the presence of multiple congenital anomalies usually associated with cases of Turner's syndrome. Though this patient had webbing of the neck, shield chest, cubitus valgus and abnormally lateral extension of the fifth finger bilaterally initially simulating Turner's syndrome, there were several features of this case that pointed away from the diagnosis of Turner's syndrome. The patient's height, 62 inches, was greater than that usually ascribed to the latter. She had no pubic or axillary hair. The bone survey revealed gracile bones with slightly increased length and marked bone retardation. This patient also had a chromatin positive or female sex chromatin pattern on skin biopsy and vaginal smear, and normal urinary excretion of the neutral 17-ketosteroids. However, the strongest argument against Turner's syndrome in this instance was the repeatedly demonstrated absence of urinary gonadotrophins.

An elevated excretion of gonadotrophins has been considered to be a necessary criterion in the diagnosis of Turner's syndrome or ovarian agenesis (22, 25). Several investigators have reported cases of "Turner's" with normal or low gonadotrophin excretion. Dorff, Appelman, and Liveson (26) reported a case of Turner's with "absent urinary gonadotrophins." However, the technique used was only a semiquantitative one, registering positive at levels of 100 mouse units or greater. In 1950, Hertz, Cromer, and Westfall (27) reported a patient with normal levels of gonadotrophins who was proven to have ovarian agenesis at abdominal explora-

tion. This patient was short in stature, but had no other anomalies. Carpentier, Stolte, and Visschers (28) reported three cases of ovarian agenesis proven at operation who had normal levels of urinary gonadotrophins. Greenblatt and Carmona (29) in 1955 reported a case of proven ovarian agenesis with normal urinary gonadotrophin titer. Hoffenberg and Jackson (24a) in 1957 mention five instances of gonadal dysgenesis with no elevation in the urinary gonadotrophins, none having the associated anomalies characteristic of Turner's syndrome. One case did not meet the pathological criteria of ovarian agenesis at operation. Two cases had normal urinary gonadotrophin titers, and one case, a 21-year-old woman, had negative gonadotrophin titers at six mouse units, vestigial ovaries at operation, and a male sex chromatin pattern. Lower titers of gonadotrophin were not tested.

Thus, in our review of the literature, only eight cases of well documented ovarian agenesis with normal levels of urinary gonadotrophins, and only one case with low levels, could be found. There were no adult cases with absent urinary gonadotrophins, as in our patient.

Our patient was a case of hypogonadotrophic hypogonadism. It is the first reported case of hypogonadotrophic hypogonadism simulating Turner's syndrome.

Summary

A case of hypogonadotrophic hypogonadism is presented that simulates Turner's syndrome. The clinical and laboratory aspects of hypogonadotrophic hypogonadism and Turner's syndrome are reviewed, and the diagnostic criteria discussed. Applying these criteria, it is shown that the patient that we have presented, though initially mimicking Turner's syndrome, is actually a case of hypogonadotrophic hypogonadism. To our knowledge, this has not been previously reported.

Acknowledgment

We are indebted to Dr. Louis J. Soffer, Chief of the Department of Endocrinology, The Mount Sinai Hospital, New York, for his valuable advice and suggestions in the preparation of this report.

Summario in Interlingua

Es presentate un caso de hypogonadismo hypogonadotrophic qu simula syndrome de Turner. Es revistate le aspectos clinic e laboratorial del duo conditiones, e le criterios diagnostic es discutite. Es monstrate, a base de ille criterios, que le hic-reportate caso—ben que simulante syndrome de Turner al initio—es de facto un caso de hypogonadismo hypogonadotrophic. In tanto que nos lo sape, isto ha non previemente essite reportate.

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Pituitary Apoplexy in a Patient with Acromegaly

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This case is presented as an instance of spontaneous destruction of the pituitary in a patient with acromegaly. Trophic hormone deficiencies were permanent and necessitated replacement therapy.

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Case Report

The patient, a 43-year-old single white female, was admitted to the University of Illinois Research and Educational Hospitals Clinics in 1949 with the complaint of bilateral breast pain and nodularity. This was diagnosed as chronic cystic mastitis. Over the succeeding two years she was given several short trials of stilbestrol therapy.

TABLE 1. Laboratory Tests Performed During Illness

Date	Serum Phosphate, mEq/liter	Serum Alkaline Phospatase	Urinary 17-keto-steroids	24-hr Radioactive Iodine	Protein Bound Iodine, μg/100 ml
5/57	2.6	1.9	5	20%	
11/57	3.0	1.5			
1/58	3.0		8		
4/59	1.6			0.05%	3.0
12/59	1.6				

She was next seen in 1954 with the complaints of intermittent edema of the eyelids and lips, acneform rash on the face and neck, and irregular menses. She was given thyroid empirically and followed in the allergy clinic until 1957. At that time the patient remarked on the increasing size of her hands and feet, which in addition to the aforementioned complaints led to a consideration of acromegaly. Detailed history revealed intermittent arthralgias, swelling of the knee joints, headaches of two to three years' duration, and cessation of her previously irregular menses.

On physical examination in 1957, the patient evidenced no acute illness. She had acneform lesions on the face, neck, and back, coarsened scalp hair, and increased hair on the lower extremities. Hands, feet, and nose were prominent as was the general muscular development. There was an increase in the interdental spaces. Periorbital and perioral tissues were thickened.

Pertinent laboratory examinations are summarized in Table 1. In addition, skull X rays revealed an enlarged sella turcica. There was no evidence of diabetes. Visual field perimetry was normal.

A diagnosis of eosinophile adenoma with decreased ovarian function was made. Despite laboratory tests, thyroid function was judged to be decreased on the basis of the clinical picture. The patient was accordingly started on a regimen of 75 μg of triiodothyronine and 2 mg stilbestrol daily. This combination was continued on an outpatient basis until the winter of 1958 when she failed to keep clinic appointments and arbitrarily ceased her medication. She returned to the clinic in June, 1958, and resumed stilbestrol alone, since previous thyroid therapy was ineffective.

By November, 1958, she felt that acral growth had ceased but complained of recurring headaches. Repeat visual field perimetry in December, 1958, revealed bilateral constriction of the superior temporal quadrants. Therapeutic intervention with surgery or X ray was advised at this time but was refused by the patient. She was therefore continued on stilbestrol.

On March 7, 1959, the patient awoke at 3:00 AM with a severe headache, particularly behind the bridge of the nose. Over the succeeding two days she developed diplopia; visual acuity decreased, and the headache persisted. On admission to the hospital, the patient denied having nausea, vomiting, and trauma. Blood pressure was 130/70 mm Hg, pulse, 70, respirations, 18. Significant physical findings were a bilateral ptosis, paresis of the right lateral rectus muscle, and a dilated right pupil fixed to light and accommodation. Visual acuity was little impaired. There was nuchal rigidity but no Kernig's, Brudzinski's, nor Babinski's signs. By March 10, there was complete right external ophthalmoplegia and periorbital edema. Lumbar puncture revealed an opening pressure of 160 mm water and sterile xanthochromic fluid containing 297 red blood cells/cm^3; protein, 117 mg/100 ml; glucose, 45 mg/100 ml; and chloride, 111 mEq/liter.

Tentative diagnoses included pituitary infarction, ruptured aneurysm of the internal carotid artery, and Guillain-Barré syndrome. The patient was transferred to the neurosurgical service for further observation. She remained alert and continued to complain of headache. An arteriogram was contemplated but on March 11, she suddenly developed a temperature of 105°F and became confused. Blood pressure fell to 90/60 mm Hg, with a tachycardia of 130. Lumbar puncture revealed clear

TABLE 2. Effect of Insulin Induced Hypoglycemia upon Urinary Porter-Silber Chromogens (March 19, 1959)

Time	Treatment	Blood Sugar, mg/100 ml	Urinary Porter-Silber Chromogens μg/gm Creatinine
8 AM–10 AM	None	92	6.5
10 AM	Regular insulin i.v.		
10:30 AM	100 gm glucose p.o.	38	
10 AM–noon	None	100	10.0
Noon–2 PM	None		16.0
2 PM–4 PM	None		13.3

TABLE 3. Effect of SU-4885 on Urinary Porter-Silber Chromogens, 17-ketosteroids, and 17-ketogenic Steroids (Borohydride Reduction), December, 1959 and June, 1960

Day	Treatment	Urinary Steroids, mg per 24 Hours		
		Porter-Silber Chromogens	17-ketosteroids	17-ketogenic-steroids
December 1959				
0	None	4.8	2.5	8.2
1	1,500 mg SU4885	2.8	2.6	5.4
2	3,000 mg SU4885	2.6	3.1	5.0
3	None	3.6	2.7	6.4
June 1960				
−3	40u ACTH			
−2	40u ACTH			
−1	40u ACTH	12.2	5.2	20.2
0	None	19.7	9.0	33.0
+1	3,000 mg SU4885	5.8	4.5	11.4
+2	3,000 mg SU4885	2.3	1.3	5.8

fluid with a pressure of 190 mm of water. Chemistries were normal and culture was negative. Cortisone was administered with dramatic response.

By March 19, diabetes insipidus was evident and myxedema was suspected on the basis of generalized pallor, bilateral periorbital edema, and constipation. Laboratory evidences of anterior pituitary deficiency are summarized in Table 1. In addition, there was no decrease in urine flow following administration of intravenous nicotine although there was an abrupt diminution following injection of vasopressin tannate. In an attempt to evaluate pituitary-adrenal function a standard glucose-insulin tolerance test was performed with concurrent measurement of urinary Porter-Silber chromogens. The results are illustrated in Table 2.

Upon her discharge in May, 1959 the headache had abated and the external and internal ophthalmoplegias had undergone spontaneous remission. Visual field perimetry revealed superior bitemporal and left inferior nasal constrictions. The patient was discharged on a regimen of cortisone, posterior pituitary snuff, thyroid extract, and cyclic estrogens.

The patient resumed her career of teaching and has required continued replacement therapy. There has been no apparent change in the size of bony structures, but the subcutaneous tissues, particularly about the face and hands, appear to be decreased. She was readmitted in December, 1959 and June, 1960 for evaluation of pituitary-adrenal function by withdrawal of cortisone followed by administration of ACTH and methopyrapone (SU-4885). The results, as seen in Table 3, suggest the absence of endogenous ACTH production (1).

DISCUSSION

Pituitary apoplexy is an infrequent event, as recorded in the literature. Survival is rare. Jefferson and Rosenthal in 1959 brought the recorded number of cases to 73 (2). Since then, three additional cases have been reported (3).

The acute clinical picture is arresting and in general pathognomic when occurring in a patient with a known pituitary tumor. The syndrome may be dominated by manifestations of meningeal irritation, ocular palsies, or hormonal insufficiencies. Therefore meningitis and ruptured aneurysm of the internal carotid artery are common initial considerations. Onset is usually by abrupt headache, often behind the bridge of the nose. This is variously followed by diplopia, loss of vision, confusion, coma, hemiparesis, dysphagia, and electrolyte disturbances. After the immediate sequelae of the catastrophe vigilance must be maintained for signs of hormonal insufficiency.

The most commonly indicated management of the acute phase is one of watchful expectation; surgical intervention may be necessary if vision is failing rapidly.

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We are grateful to Dr. C. H. Sullivan of Ciba Pharmaceutical Products, Inc., for providing the SU-4885 [(2-methyl-1, 2 bis-3-pyridyl)-1-propanone].

SUMMARIO IN INTERLINGUA

Un juvene femina con acromegalia e allargamento del sella turcic suffreva de subite mal de

capite e manifestava un rapide disveloppamento de ophthalmoplegias externe e interne. Intra un breve periodo de tempore illa disveloppava diabete insipide e signos de carentia de hormon thyroido-stimulante e de ACTH. Su defectos oculomuscular se meliorava spontaneemente. Le carentias hormonal persisteva e requireva therapia de reimplaciamento. Un certe melioration occurreva in le manifestationes acromegalic in le tissu molle, sed isto esseva accompaniate de nulle resolution ossee. Le effectos de SU-4885 super le function pituitario-adrenal esseva studiate. Le resultatos supportava le impression clinic de carentia de ACTH.

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Pulmonary Alveolar Proteinosis

A Case with Cardiac Catheterization and Pulmonary Function Studies

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In June 1958 the first description of an unusual lung disease, pulmonary alveolar proteinosis, was published (1). This original report concerned 24 cases from the United States and one each from Canada, England, and Italy. Since this publication ten additional cases have appeared in the literature (2–8) and one additional case alluded to (5). Of these 37 cases, 17 have included some data on pulmonary function studies and two were evaluated by cardiac catheterization.

Since July 1957 we have had the opportunity of following the clinical course of one of the patients originally reported (1), Case 13, and have obtained both cardiac catheterization and extensive pulmonary function tests. These detailed studies make this case worthy of publication. Continuous clinical observation of 33 months also contributes needed data concerning the natural clinical evolution of this newly described pathological entity.

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Case Report

A 34-year-old white bakery routeman had a chest roentgenogram taken by a mobile unit in July 1957 and was subsequently referred to his private physician. A two-meter posteroanterior view of the chest (Figure 1) disclosed bilateral pulmonary infiltrations.

On referral to one of us the patient was hospitalized for diagnostic evaluation and therapy. Interrogation revealed the presence of an occasional sharp, cramp-like pain in the left side of his chest associated with dyspnea, night sweats, and anorexia.

He had been asymptomatic until 1955 when he was hospitalized for one week because of a virus infection of the lungs manifested by cough and pain. A chest roentgenogram taken at this time was reported by the patient as having been normal.

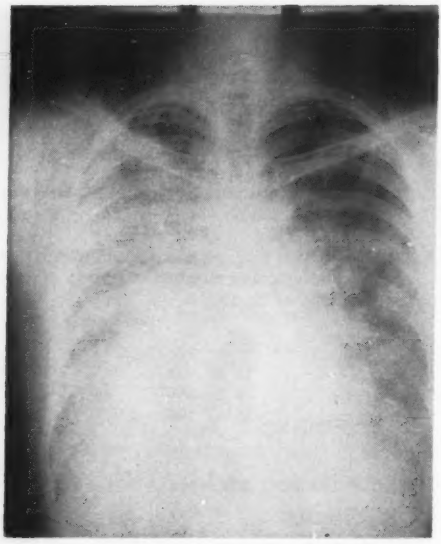


FIGURE 1. Posteroanterior chest X ray, July 23, 1957. Bilateral soft, confluent, feathery densities are present about the hilar and medial portions of the lungs, more marked on the right. The periphery of the lung fields is relatively clear. The involvement is suggestive of pulmonary edema; however, there is no apparent cardiomegaly.

About May 1957, he gradually became aware of progressive weakness and dyspnea, and of a chronic productive cough. There had been a 25 pound weight loss in the preceding two years and a long history of smoking two packages of cigarettes per day.

The patient was six feet tall and weighed 146 pounds. He was in no acute distress at admission on July 24, 1957. His temperature was 99.6 F, pulse, 104, and respirations, 28. Physical examination disclosed only a few moist râles at the lung bases. No evidence of cyanosis, clubbing of the fingers, lymphadenopathy, hepatomegaly, or splenomegaly was noted. Laboratory data on admission were: white blood cells, 9,450/mm^3 with a normal differential; hemoglobin, 16.7 g/100 ml; red blood cells, 5,600,000/mm^3; and hematocrit, 47%. Examination of the urine revealed a 2+ reaction for protein, and the erythrocyte sedimentation rate was 27 mm/hour (Wintrobe). The serum albumin was 5.1 g/100 ml, and globulin, 2.7 g/100 ml. On serum electrophoresis the globulins were as follows: alpha$_1$, 6.05%; alpha$_2$, 19.6% (elevated); beta, 8.1%, and gamma, 12.8%. The thymol turbidity, cephalin-cholesterol flocculation, cholesterol, and alkaline phosphatase determinations were within normal limits as were the serum electrolytes (sodium, potassium, chlorine, and calcium), plasma carbon dioxide combining power, and serum protein bound iodine determinations. Examination of the electrocardiogram revealed mild sinus tachycardia and a QRS vector directed vertically and slightly posteriorly. Polyagglutination studies (typhoids, paratyphoids, heterophil, *Brucella abortus*, and *Proteus OX-19*), lupus erythematosus cell test, and smears and cultures for bacteria, fungi, and tuberculosis were non-contributory. The intradermal skin test for histoplasmosis was negative; the intermediate strength purified protein derivative was 1+. Bronchoscopy disclosed a large amount of secretion.

Cytological and bacteriological examinations of this material were negative. Left scalenus node biopsy revealed reactive hyperplasia. Pulmonary function tests (Table 1) were consistent with an alveolar capillary diffusion defect. A surgical biopsy of the middle lobe, right lung (Figure 2) disclosed minimal thickening of the visceral pleura, and thin alveolar septa containing small capillaries without fibrosis or inflammatory reaction. Most of the alveolae were filled with a homogeneous, amorphous, acidophilic material which appeared to be protein. A dilated peripheral lymphatic and terminal bronchiole also contained protein material. The pathological diagnosis was "proteinoid pneumonopathy, etiology undetermined." Tissue submitted to the Armed Forces Institute of Pathology for comparison with a group of similar cases known to be under study there led to the inclusion of this case in the published study (1). Postoperatively the patient was started on cortisone (100 mg/day) which was later reduced by 50%. Subsequently, antibiotic therapy was added.

Essentially unimproved, he was hospitalized elsewhere in October 1957. Additional studies proved to be unrevealing. Because of a daily fever spike, penicillin was administered and later, when specimens from the respiratory tract grew out pure cultures of *Candida albicans*, mycostatin was added to the regimen. In November cortisone therapy was discontinued and after ten days the patient was sent home and instructed to continue oral penicillin, mycostatin, and isopropylarterenol aerosal. While on this regimen the patient gradually improved and the dyspnea decreased. In December there was slight ankle edema and the patient discontinued the penicillin therapy. At the end of six weeks he returned to the hospital; his condition was essentially unchanged. After being discharged he was given mycostatin medication which he continued for two months.

In April 1958 he was seen at the Veterans Administration Hospital, Omaha. At this time he weighed 179 pounds and complained of mild exertional dyspnea and a chronic cough which produced a half cupful of a whitish mucoid sputum per day. Routine laboratory tests and the appearance of the chest film (Figure 3) were essentially the same as previously. In May, because of afternoon fever, sweating, soreness in the anterior chest, and expectoration of one-fourth cupful of brownish sputum per day, he was given a course of sulfonamide therapy and experienced symptomatic relief. When

TABLE 1. Pulmonary Function Tests

Tests and Units	Estimated Normal	Actual Value: June 1957	April 1959	May 1960
Age (yrs.)	—	34	36	37
Height (inches)	—	72	72	72
Inspiratory capacity (liter)	3.8 (12)		2.48	2.53
Expiratory reserve vol. (liter)	.8 (12)		1.70	1.60
Vital capacity, 2 stage (liter)	4.26 (13)		4.18	4.13
As % of predicted (%)	>85. (13)		98	97.
Maximal breathing capacity (liter/min)	117. (13)		75.5	129.6
As % of predicted (%)	>80. (13)		64.4	111
Vital capacity, 1 stage (liter)	4.26 (13, 14)	2.3	3.60	4.04
*Timed percentage, 1 sec (%)	>72. (14)	70	77	64
2 sec (%)	>88. (14)		93	86
3 sec (%)	>92. (14)		96	93
Maximal inspiratory flow (liter/sec)	6.4 (12)		3.35	
Maximal expiratory flow (liter/sec)	5.2 (12)		3.18	
Total range of maximal flow (liter/sec)	11.6 (12)		6.53	
Maximal mid tidal inspiratory pressure	>40. (12)		55	
With "calibrated leak" (mm Hg)	>35. (12)		31	
Maximal mid tidal expiratory pressure	>40. (12)		70	
With "calibrated leak" (mm Hg)	>35. (12)		40	
Total range of mid tidal maximal pressures (mm Hg)	>75. (12)		125	
With "calibrated leak" (mm Hg)	>65. (12)		71	
Gas trapping	none (13)		none	
Weight (pounds)	—	147	187.	197
Body surface area (meter^2)	—		1.87	
Tidal volume (liter)	.56 (11, 12)		1.19	
Respiratory rate (#/min)	14. (11, 12)		14.	
Minute vol. (liter/min)	7.8 (11)	37.0	16.7	
Functional residual capacity (liter)	2.0 (11, 12)		2.78	
Total lung capacity (liter)	5.46 (11, 12)		5.25	
Residual vol. (liter)	1.20 (11, 12)		1.08	
As % tot. lung cap. (%)	22 ± 10 (13)		21.	
Gas distribution by:				
Fowler single breath† (% change)	<2.5 (15)		1.8	
Time to "equilibrium"† (min)	<2.5–3.(12)		2.3	
O_2 utilization† (liter/min)	—		.42	
Ventilatory equivalent for O_2† (liters/liter)	23.3 (13)		57.7	
Elastance‡	8.9 (12)		11.3	
Capacitance‡	.11 (12)		.088	
Resistance‡	4.5 (12)		5.6	
End tidal PCO_2 (mm Hg)	43 (16)		35.5	
Saturation,§ resting (%)	97	92.0	98.5	98.5
Mild exercise (%)	97	86.0	97.	
Breathing O_2 (%)	99	100.0	98.5	

Numbers in parentheses refer to references.

The reference following each of the estimated normal values indicates both a reference to the method used and to the standards, usually by sex, age, and size. For convenience each value is compared with its estimated normal value as of April 1959.

* The percentage timed vital capacity is calculated on the basis of the single stage vital capacity actually achieved on that date, and not on the predicted.

† Time to equilibrium, O_2 utilization, and ventilatory equivalent were all measured during the functional residual capacity determination by the closed circuit equilibration method (nitrogen meter).

‡ These values are for total respiratory elastance and capacitance by the method of passive inflation, and resistance by the method of sinusoidal pressures, and are therefore to be contrasted with, not equated to, values for the lung alone obtained by esophageal balloon techniques.

§ Saturation by ear oximetry; for resting saturation by Van Slyke see Table 1.

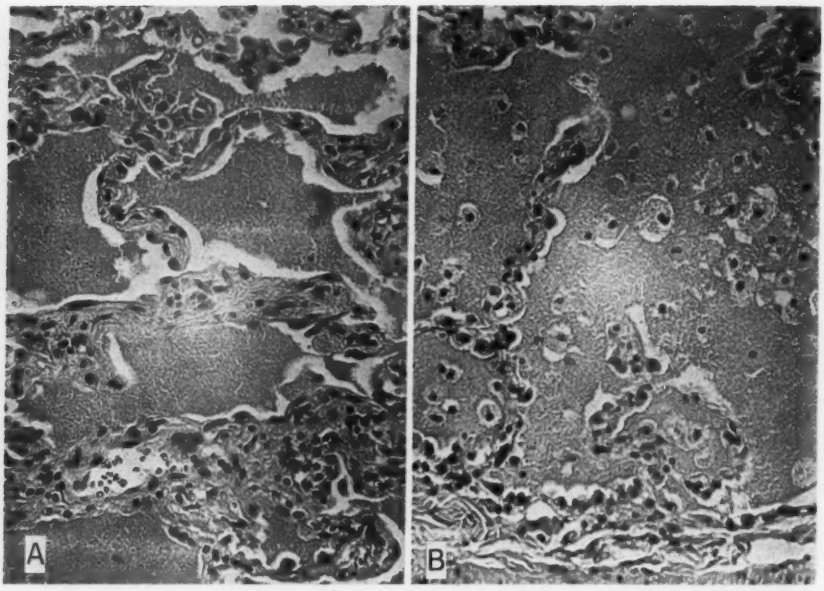


FIGURE 2. Photomicrographs of biopsy specimen taken from the middle lobe, right lung on July 10, 1957. Figure 2 (A) represents a magnification of × 220; Figure 2 (B) ×340. An amorphous, homogeneous, acidophilic proteinaceous material fills most of the alveolae. The septa contain many small capillaries without any evident fibrosis or inflammatory reaction. (Courtesy Dr. Earl Green, Pathologist at Bishop Clarkson Memorial Hospital, Omaha, Nebraska.)

re-evaluated in September (Figure 4) the patient had slight chest pain and exertional dyspnea. In January 1959, because of continuing fatigue, weakness, and cough, the patient was hospitalized. On physical examination there was a postnasal discharge and injection of the posterior pharyngeal wall, increased posteroanterior diameter of the chest, generalized hyperresonance (except for dullness at the bases posteriorly), inspiratory and expiratory râles at the bases posteriorly, and audible wheezing in the right anterior paramediastinal area. The blood pressure was 155/95 mm Hg and the pulse was regular at 92/minute. There was no evidence of clubbing, cyanosis, or arthropathy. Of special interest were a 16% bromsulphalein retention at 45 minutes; a 19 mEq/liter serum carbon dioxide content; and a normal leukocyte count with 40% lymphocytes on differential study. Results of extensive laboratory procedures were essentially negative otherwise. Steroid and antibody therapy was not reinstituted either during or following this hospitalization.

In March, 1959 he was hospitalized for further cardiopulmonary evaluation. The results of the physical examination were similar to those noted in January. The leukocyte count was 6,550/mm^3 of which 57% were lymphocytes. Other determinations (urinalysis, hemoglobin, hematocrit, and erythrocyte sedimentation rate) were negative. The serum electrolytes were also within normal limits. Electrocardiography demonstrated some changes during the period of observation since the patient's had shifted from an initial plus 90° to a 60° axis initial examination in 1957. The mean QRS vector in the frontal plane and concomitantly the mean T wave vector had shifted from an initial plus 70° to a 30° axis in the same plane. These changes, however, were of questionable significance, especially in view of the 40 pound weight increase during this interim. Cardiac catheterization and pulmonary function tests revealed questionable, or, at most, mild abnormalities (Tables 1 and 2). Roentgenograms gave no evidence of significant changes from those of September 1958 (Figure 4).

Feeling improved, the patient obtained a full-time job tending parking meters. He has been seen periodically in the outpatient department and continues to be asymptomatic. His last roentgenogram on April 28, 1960 (Figure 5) disclosed further clearing of the lung fields.

DISCUSSION

The pathological findings in pulmonary alveolar proteinosis have been discussed extensively in the publication of Rosen et al. (1). They reported that in most sections of the

involved portions of the lung, the microscopic appearance of the alveolar membranes, blood supply, lymphatic drainage, bronchiolar mucosa, musculature, and supporting tissues was within normal limits. In most instances, however, the alveolar spaces were filled with a proteinaceous granular material with deeply staining laminated bodies. These authors thought that this material was "formed by a remarkable transformation of large mononuclear cells in the walls of alveoli—the so-called 'septal cells'." It was suggested that the changes noted in pulmonary alveolar proteinosis might be due to a hypersensitivity re-

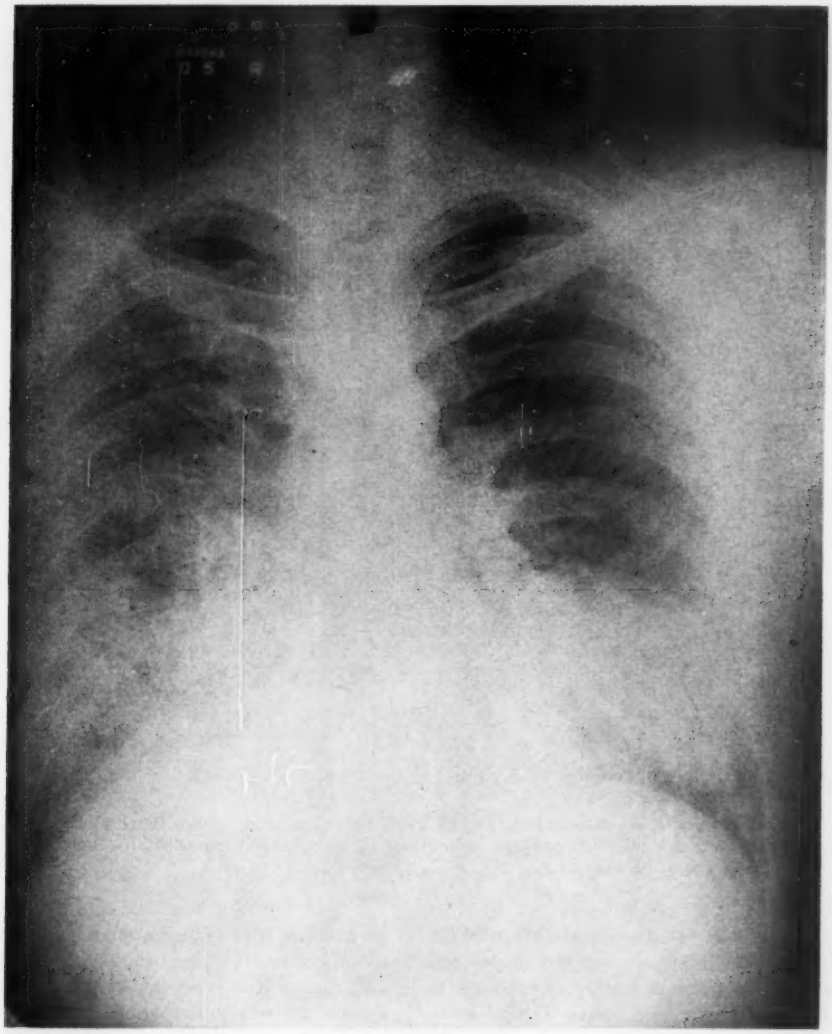


FIGURE 3. Chest X ray taken on April 9, 1958. The heavy confluent infiltration continues to involve both lower lung fields and extends into the right upper lung field. A dense infiltration now extends to the periphery of the left lower lobe; however, there is some clearing in the left upper lobe and in the periphery of the right lung.

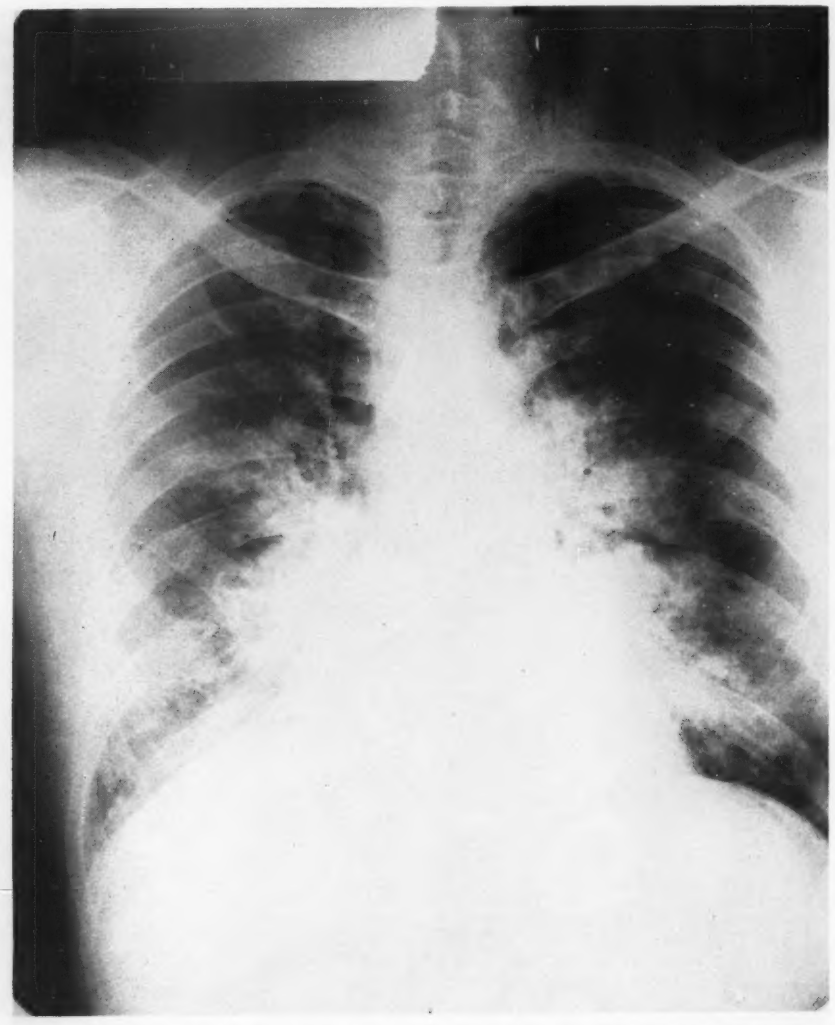


FIGURE 4. Chest X ray taken on October 24, 1958. There has been further clearing bilaterally; however, there are residual confluent infiltrations in the medial portions of the lung fields, particularly about the hilar areas.

action. This was based upon the eosinophilic infiltration noted in some of the biopsy material and the frequent history of exposure to wood dust, solvents, and sprays. Typical histological findings (Figure 2) were noted in our case; however, neither eosinophilic infiltration nor any history of such exposure was found.

In view of the limited number of cases reported and the relatively short duration of follow-up studies of up to five years the course and natural history of this disease are not yet known. Its course has varied from apparent complete recovery to a rapid fatal course of four months' duration (1). To date, nine of these patients have died. Although symptomatic improvement has occasionally been reported,

TABLE 2. Cardiac Catheterization Data

	Pressure Readings (mm Hg)							O_2 Consum. (cc/min)	Ear Lobe Oximetry (sat %)	O_2 cont. (vol %) / O_2 sat (%)			Card. Output (L/min)	Resistances (dynes sec/cm^5)		
	SVC (m)	RA (m)	RV s/d	RV m	PA s/d	PA m	RPAW (m)			FA	PA	RPAW		Total Peripheral	Total Pulm.	Pulm. Vasc.
Resting	3	3	(20–25) / (4–6)	10	(20–25) / (4–10)	15	5–8	362.6	98.5	20.17 97.9%	14.46 63%	 100%	6.35	998	187	100
After moderate exercise			(20–35) / (4–6)		(20–35) / (5–15)	20		520.0	97.0							
			Return to normal level after 3 min. resting													
8 min. after inhaling 100% O_2			(20–25) / (4–6)	10	(20–25) / (5–10)	15			98.5							

SVC = superior vena cava; RA = right atrium; RV = right ventricle; PA = pulmonary artery; RPAW = right pulmonary artery wedge. (See text for discussion.)

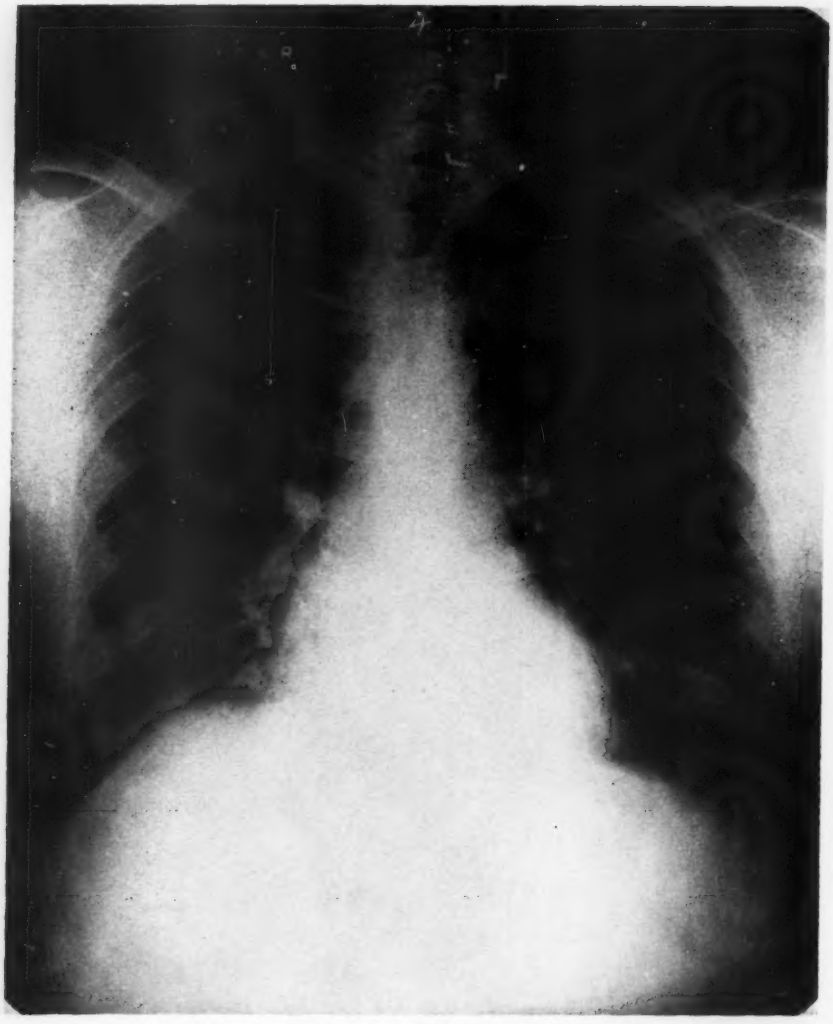


FIGURE 5. Chest X ray taken on April 28, 1960. Additional clearing has occurred; however, there remain some patchy fibrotic-appearing infiltrations in the mid and lower lung fields.

the majority of cases showed no significant relief following antibiotic or steroid therapy, or both (1, 9). Dramatic symptomatic improvement, however, has occasionally been reported (3). The late stage of this disease has usually been complicated by infections due to staphylococcal, fungal, and other virulent pathogens associated with, and perhaps secondary to, antibiotic or steroid therapy. The terminal phase in these patients was characterized by severe dyspnea and cyanosis due to blockage of the respiratory surface, probably by the proteinaceous materials.

In this case, complete pulmonary function tests performed in April 1959 (Table 1) revealed only a few abnormalities which suggested a rather mild dysfunction predominantly obstructive in type; even these subsequently disap-

peared. Initially, however, in June of 1957, the pulmonary dysfunction had been much more severe, suggestive of restriction rather than obstruction to the ventilation, and with diffusion and shunt abnormalities of a type compatible with pulmonary alveolo-capillary blockade.

In June 1959 the total vital capacity was markedly reduced below normal to 2.3 liters, approximately 53% of the predicted value. The test of timed forced respiration performed, viz., the 1 second timed vital capacity was 70% of this, which was nearly within normal limits. These findings suggest a restriction of ventilation without obstruction. Diffusion defect was suggested by the finding of desaturation of the arterial blood at rest, which was accentuated by exercise and eliminated the inhalation of oxygen. Right to left shunts may also have been present, since the report of the 100% saturation of arterial blood by oximetry with the patient breathing pure oxygen does not eliminate this possibility. These findings plus the hyperventilation at rest (37 liters per minute) were the initial findings compatible with alveolo-capillary blockade.

In April 1959 the maximal breathing capacity was approximately two-thirds of the normal range and the maximal respiratory flow rate was just less than three-fifths of that predicted. Maximal ventilatory pressures, suggested as a measure of respiratory strength, and the two-stage vital capacity were within normal limits; the one-stage vital capacity was somewhat reduced. Respiratory stiffness (elastance) was but slightly increased. These findings form a pattern suggestive of mild respiratory obstruction rather than one of restrictive functional changes. In this patient, however, the respiratory resistance, the residual volume, and the measures of gas distribution within the lungs were within normal limits. There was no evidence of gas trapping recorded during the test for maximal breathing capacity, nor could it be demonstrated by maximal expiration near the point of equilibration during measurement of the functional residual capacity (closed circuit, nitrogen meter method). These findings are contrary to the concept of an obstructive lesion of the emphysematous type. Diffusion, although apparently impaired two years previously, was not significantly impaired now, as judged by Shephard's criteria regarding the arterial saturation at rest, on exercise, and after breathing oxygen (10). Even if right to left shunts accounted for part of the initial dysfunction, they could not have been of significant size at the time of these tests. Initially, oximetry at rest demonstrated 92% saturation; now it was 98.5% and the Van Slyke arterial saturation was 97.9% (Tables 1 and 2).

These dysfunctions suggested that a restrictive lesion had been present initially; and that the process causing this restriction had also affected the pulmonary circulation and had caused the diffusion defect with or without shunt defects. The pathological findings characteristic of this disease, namely, filling of a fraction of the alveoli with proteinoid material, could explain all of these initial dysfunctions. Compensation might then have occurred in part by overventilation and overperfusion of the uninvolved alveoli and by underperfusion of the involved alveoli. From the aspect of ventilatory mechanics, the obliteration of a fraction of the alveolar space by proteinoid inclusion should have produced a restrictive lesion initially. The pulmonary involvement could have been modified during the intervening years by both healing and compensatory processes. Compensation in the range of respiratory volumes could have been achieved by the patient despite continued stiffness within that range of motion, thus permitting better ventilation at the cost of an additional burden on the musculature. Between April 1959 and April 1960, this functional compensation became virtually complete despite the continued involvement demonstrated by X rays. The initial syndrome postulated here, i.e., restrictive lesion with alveolar capillary block and possibly right-to-left shunting, is similar to that in the only severe cases previously published (1, 3, 9) in sufficient detail.

Cardiac catheterization studies have been reported (1) in two patients with alveolar proteinosis. One was normal and the other indicated a marked oxygen desaturation of the peripheral arterial blood, moderate pulmonary hypertension, and high cardiac output. After inhalation of 100% oxygen, the arterial oxygen saturation promptly returned to normal, the pulmonary artery pressure was lowered, and the cardiac output was significantly reduced. Presumably, the arterial hypoxia was due to pul-

monary alveolar block. In our patient (Table 2) normal findings were noted except possibly for the slightly increased fluctuation of right heart pressure during the different phases of respiration at rest. The pulmonary artery wedge pressure was normal. After moderate exercise there was a transitory minimal elevation of pulmonary artery pressure, which returned to pre-exercise level after three minutes. This represents a mild abnormality. The absence of arterial oxygen desaturation with exercise was again noted during catheterization studies; its importance in helping to exclude a significant degree of diffusion or shunt defect has been discussed.

Summary

The natural history and physiopathological involvements of the clinical syndrome of pulmonary alveolar proteinosis recently described can only be elucidated by long-term follow-up studies, preferably of patients seen early in the course of this disease. This paper describes the clinical course, detailed pulmonary function studies, and catheterization in a patient with severe early pulmonary findings who has been followed for 33 months since the onset of his illness, and who has manifested considerable improvement by clinical and functional criteria during that time.

Summario in Interlingua

Le historia natural e le affectiones physiopathologic del syndrome clinic de proteinosis pulmono-alveolar (que ha recentemente essite describite) pote esser elucidate solmente a base de prolongate studios catamnestic, preferibilemente in patientes vidite precocemente in le curso del morbo. Le presente communication describe le curso clinic e presenta detaliate studios de function pulmonar e de catheterismo cardiac in le caso de un patiente con precocemente grave constatationes pulmonar qui ha essite sub observation depost 33 menses a partir del declaration del morbo e qui ha manifestate un considerabile melioration in le curso de ille intervallo secundo criterios clinic e etiam functional.

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Vaccinia Gangrenosa

Report of a Case and Review of the Literature

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VACCINIA GANGRENOSA IS A RARE COMPLICATION of smallpox vaccination characterized by progressive spread and necrosis of the primary inoculation site, metastatic vaccinial lesions, sometimes occurring in multiple outcroppings, and a uniformly fatal outcome when not specifically treated. Of the several important complications of smallpox vaccination, it is the least common and has the poorest prognosis. The following case is the twelfth to be reported fully in the literature in English, the third involving an adult, and the third in which the disease itself was not fatal.

CASE REPORT

A 58-year-old white man was admitted to The New York Hospital on March 24, 1959, with redness and swelling of his left upper extremity of five days' duration.

Eight years prior to admission, the patient was found to have chronic lymphatic leukemia. He had received three courses of X-ray therapy, the last one three years prior to admission. He had received 2 mg of chlorambucil per day for five months prior to admission, and 10 mg of prednisone per day since an episode of hemolysis secondary to the leukemia two years prior to admission. During the several months preceding admission, his total leukocyte count had been relatively stable, ranging from 24,000 to 33,000/mm^3, and he had been essentially asymptomatic, as indeed he had been since the onset of the disease.

The patient had been vaccinated in childhood, and had reacted in a routine manner. Sixteen days prior to admission, in preparation for a trip to Europe, he had received a smallpox inoculation in his left arm, his first since childhood. Within the next three days, he noted mild swelling, erythema, and pruritus around the inoculation site. His attention was not again drawn to the arm until five days prior to admission, when he awoke to find the entire arm swollen and red. It was not painful, tender, or warm. He felt chilly, perspired persistently and profusely, and had oral temperatures ranging from 101 to 104 F. During the next several days, the swelling and erythema progressed to involve the forearm, reaching but not passing the wrist, and the inoculation site turned black over an area several centimeters in diameter. He applied boric acid soaks to the extremity during the three days prior to admission and on the day before admission took three tablets containing tetracycline and mycostatin; neither treatment was thought by the patient to have been locally or systemically effective.

The patient had been told an indeterminate number of years before that he was allergic to chocolate, but he did not recall ever having had a reaction to this food and could not recall the last time he had eaten it. He knew of no other allergies or past allergic phenomena involving either himself or his family. Between 13 and 28 years prior to admission, he had had approximately six episodes of migrating polyarthritis, the cause of which was never diagnosed.

On physical examination, the patient was well developed, well nourished, and appeared acutely and chronically ill. His blood pressure was 104/62 mm Hg; pulse 92/min and regular; respirations 30/min; and there was a rectal temperature of 40.2 C. The left upper extremity was moderately edematous and the skin was purplish-red from the axilla to the fingertips. The site of inoculation was necrotic and black, and was surrounded by a 10 by 16 cm area of greenish-colored bullae. Erythema extended from the axilla down the left lateral chest wall for several centimeters. The involved region was

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not painful or tender, and perceived sensation. Other positive findings were the unaltered signs of his leukemia, which included several 2 by 2 cm lymph nodes in the anterior cervical and right axillary regions, a liver edge palpable 21 cm below the right costal margin in the midclavicular line, and a spleen palpable 9 cm below the left costal margin in the midclavicular line.

The hemoglobin was 14.3 g/100 ml, the red blood cell count, 5.2 million/mm^3, and the white blood cell count, 8,200/mm^3, of which 76% were lymphocytes, 8% mature neutrophiles, 14% band forms, 1% monocytes, and 1% eosinophiles. Platelets were moderately depressed on the peripheral blood smear. Urinalysis was normal except for three to six white blood cells per high power field. A chest X ray was negative.

Vaccinia virus was demonstrated by its cytopathogenetic effect on monkey kidney monolayer culture, rabbit kidney monolayer culture, and HeLa cells, as well as by the inhibition of its effect on HeLa cells by vaccinia hyperimmune rabbit serum. The virus was cultured from vesicular fluid, but not from blood or urine collected prior to specific treatment. Paper electrophoresis revealed normal serum albumin, $alpha_1$ globulin and $alpha_2$ globulin fractions, and decreased $beta_1$ globulin and gamma globulin fractions. The gamma globulin level was demonstrated to be 60% of its normal lowermost limit, with a decrease in both the 7S and 19S fractions. Neutralizing antibody against the vaccinia virus could not be demonstrated in blood taken five days after admission; it was present in a titer of 1:4 12 days after admission. Circulating neutralizing antibody, presumably passively transferred, was found in a titer of 1:8 in blood drawn 34 and 40 days after immunization, and in a titer of 1 : 16 52 and 54 days after immunization.

During the first four hospital days, the bullous area regressed, but the erythema moved further down the left lateral chest wall. Both the temperature and the white cell count decreased, the former falling to between 37 and 39 C. The patient was treated on the third hospital day with 10 ml of hyperimmune vaccinial gamma globulin, and on the fourth, fifth, and eighth days with 300, 400, and 600 ml, respectively, of hyperimmune vaccinial whole blood. On the fifth day, one papular and four vesicular lesions appeared on the right leg and left leg, respectively. These were the only metastatic lesions to appear; they did not progress, and began to regress two days later. During the remainder of the course, the edema, erythema, and bullae regressed, the latter becoming replaced by an 11 by 15 cm eschar, which reached its peak size on hospital day 11. After day four, the rectal temperature was maintained essentially between 37 and 38 C, and the white blood cell count continued its gradual decline to preadmission levels. The eschar was debrided on day 21, and there were no further complications of the vaccinial disease.

Several days later, however, he developed pneumonic changes thought to be wholly explainable by a demonstrated staphylococcal pneumonia. He died 77 days after admission of respiratory insufficiency and cardiovascular failure.

At post-mortem examination, he was found to have disseminated bronchogenic carcinoma. The findings were primarily those of disseminated cancer and chronic lymphatic leukemia, and manifestations of the vaccinia and of the staphylococcal pneumonia were either masked or absent. The spleen contained congested sinusoids, indistinct germinal centers, and an increased number of mature lymphocytes in the white pulp. The lymph nodes were replaced by metastatic tumor tissue.

Discussion

Vaccinia gangrenosa differs from generalized vaccinia, a more common complication of smallpox vaccination, by the progressive enlargement and necrosis of the vaccination site, by the usual appearance of successive outcroppings of secondary lesions, and by the characteristically fatal outcome. Generalized vaccinia, in contrast, is typically self-limited, without spread of the primary site, and with no more than one or two outcroppings of metastatic lesions.

PATHOGENESIS

Depressed antibody response would appear to be a *sine qua non* for the occurrence of vaccinia gangrenosa. In each of the seven cases, including the one reported here, in which conclusive studies were performed, the antibody titer against the vaccinia virus was found to be absent (see references 4, 6, 7, 9, 12, 13, and present case in Table 1). The differences between this entity and generalized vaccinia are readily explainable on this basis. Viremia occurs

TABLE 1. Previously Reported Cases of Vaccinia Gangrenosa *

Author	Age	Sex	Interval Between Vaccination and First Observed Secondary Lesion	Duration of Disease	Treatment	Result	Serum Gamma Globulin	Serum Neutralizing Antibody	Comment
Acland and Fisher (1)	3 mo	?	?	8 wk	?	Death	N.D.	N.D.	Areas of necrosis in liver and spleen at post-mortem.
Shortt (2)	3 mo	M	16 days	27 days	None	Death	N.D.	N.D.	
Conybeare (3)	31 yr	M	?	10 mo	?	Death	N.D.	N.D.	
Crosbie and Downie (4)	11 mo	F	?		100 ml HVB on day 55†	Lesions almost healed 17 days later. Died on day 88 of mastoiditis.	N.D.	O	
Bigler and Slotkowski (5)	5½ yr	F	?	5 wk	Various antibiotics	Death	N.D.	N.D.	
Laurance et al. (6)	4 mo	F	21 days	83 days	Various antibiotics	Death	O	O	Vaccinia virus cultured from liver, spleen, bone marrow, blood. Diffuse visceral necrosis. No cellular reaction.

* Legends:

N.D. = not done.
HVB = hyperimmune vaccinial whole blood.
HVG = hyperimmune vaccinial gamma globulin.
GG = gamma globulin.

† All "days" are in relation to vaccination date.

TABLE 1 (*Continued*)

Author	Age	Sex	Interval Between Vaccination and First Observed Secondary Lesion	Duration of Disease	Treatment	Result	Serum Gamma Globulin	Serum Neutralizing Antibody	Comment
Keiden et al. (7)	8 wk	F	2 wk	7 wk	60 ml. HVG, 1 mo; 250 ml HVB, 9 wk; 500 mg and 200 mg GG 10 wk and 10 wk, 1 day, respectively.	Death	O	O	An axillary lymph node contained many monocytes and plasma cells and no germinal centers or lymphocytes. Spleen contained few malphigian corpuscles; these contained plasma cells and monocytes, but no lymphocytes.
Kozinn et al. (8)	3 mo	M	14 days	1 mo	20 ml GG and 260 ml HVB begun on day 24; ACTH, day 28; cortisone, day 33.	Death	N.D.	Results inconclusive due to prior treatment	Diffuse visceral necrosis at post-mortem. No lymphadenopathy. Mesenteric lymph node contained no germinal centers; lymphocyte-predominant cell.
Barbero et al. (9)	5 yr	M	2½ mo	91 days	7 ml HVG, day 87; 10 ml, days 91, 109, and 123.	Recovery	Normal	O	Previous undiagnosed disease of reticuloendothelial system. Depressed antibody response to various antigens.

TABLE 1 (*Continued*)

Author	Age	Sex	Interval Between Vaccination and First Observed Secondary Lesion	Duration of Disease	Treatment	Result	Serum Gamma Globulin	Serum Neutralizing Antibody	Comment
Olansky et al. (10)	42 yr	F	3½ wk	42 days	GG; cortisone	Death	"Slightly low"	N.D.	Chronic lymphatic leukemia.
Carson and Donnell (11)	9 mo	M	15 days	84 days	330 ml GG; 1,645 ml immune plasma; 585 ml HVG; prednisone.	Death	?	O	
Somers (12)	6 mo	M	?	15 wk	Vaccinia GG, 250 mg per day for 9 days.	Death	O	Decreased (det'mn. made after treatment and amount present could have been passively transferred).	
Lewis and Johnson (13)	8 mo	F	10 days	41 days	10 ml polio immune GG, day 29; 10 ml, 20 ml, 10 ml, 10 ml vacc.-immune GG days 27, 34, 38, and 41, respectively; ACTH.	Death	O	O	
Present Case	58 yr	M	20 days	Regression began on day 20	10 ml HVG and 300 ml, 400 ml., and 600 ml HVB on days 18, 19, 20, and 23, respectively.	Recovery	Decreased	O	Chronic lymphatic leukemia.

normally six to eight days after routine vaccination (14). It is at this time that the lesions in generalized vaccinia usually appear. Humoral antibodies to the vaccinia virus appear one week following vaccination, gradually increase in titer during the next two weeks, and reach a peak at the end of the third week (15). The antibody response is responsible for the accelerated development, healing, and termination of the skin lesions and for the good prognosis in generalized vaccinia. In the absence of antibody, the viremia and attendant visceral destruction are allowed to continue unimpeded.

A more precise definition of the pathogenesis of vaccinial infection is suggested by Fenner (16), who demonstrated the striking similarity between the virus of infectious ectromelia in mice and the vaccinia virus and the diseases produced by these agents, and who also delineated the pathogenesis of the mouse disease. Within eight hours of the inoculation of a few virus particles into the skin, the regional lymph nodes were found to contain the virus. Upon necrosis of the cells in the node, the virus appeared in the blood, only to be immediately sequestered by the phagocytes of the liver and spleen. After multiplication at these sites, secondary viremia occurred, followed soon by skin lesions. Multiplication continued at the original site, in the spleen, the liver, and the secondary skin lesions, and was checked in some animals only by the appearance of circulating antibody, which also prevented the virus from infecting new cells.

The absence of lymphoid reaction centers noted independently by Keiden, McCarthy, and Haworth (7), and by Kozinn, Sigel, and Gorrie (8), is now recognized as the characteristic response of agammaglobulinemic patients to an antigenic stimulus (17). That depressed lymphoid reaction is not of particular significance in the pathogenesis of vaccinia gangrenosa is indicated also by the fact that this lack of response was not found in other patients. In contrast to the patients of Keiden et al. and of Kozinn et al., two of those reported by others (9, 13) had an absolute lymphocytosis. The observation by Keiden et al. of increased numbers of plasma cells in the lymph nodes and spleen of their patient is of interest, as antigenically stimulated agammaglobulinemic patients typically have the opposite reaction (17). If the view of some investigators (18) that "the plasma cell family is a specific response to antigenic stimulation and is engaged in antibody synthesis whenever encountered" is correct, the prevalence of plasma cells in the reticuloendothelial tissue of their patient, associated with the absence of circulating antibody, would suggest that antibody was being produced but was either destroyed or was not released. Marshall and White (19) observed a decrease in lymphocytes and an increase in plasma cells in the spleens of rabbits injected intravenously with various antigens. It is possible that, in the absence of antibody response, the circulating antigen in the agammaglobulinemic patient may act as a persistent antigenic stimulus, and, in addition, that the increased plasma cell response represents a compensatory effort on the part of the reticuloendothelial tissue to produce antibody. Many objections might be raised to this hypothesis, however, not the least of which would be the absence of such a response in other antigenically stimulated agammaglobulinemic patients.

The essential differences in the postmortem findings in vaccinia gangrenosa and in generalized vaccinia are, as might be expected, the more extensive visceral necrosis and the decreased or absent healing response found in vaccinia gangrenosa (20, 21).

ETIOLOGIC CONSIDERATIONS

This is the third adult case of vaccinia gangrenosa in the English literature, and

the second with underlying chronic lymphatic leukemia. The association is almost certainly due to the high incidence of hypogammaglobulinemia and altered antibody responsiveness in patients with chronic lymphatic leukemia (22). Vaccination of patients with this and other diseases known to be associated with hypogammaglobulinemia should be considered a dangerous procedure and should be performed only with full appreciation of the hazard involved.

Idiopathic agammaglobulinemia, whether congenital or acquired, is the other entity which predisposes to the occurrence of vaccinia gangrenosa. This is presumably due to the invariable depression of antibody responsiveness associated with this condition. It is of considerable interest that most agammaglobulinemic patients have a normal primary response to vaccination, and, indeed, develop an immune response on repeat vaccination despite the absence of detectable serum antibodies (23, 24). It is apparent that other factors, as yet unknown, play a significant role in the etiology of vaccinia gangrenosa, and that depressed antibody response does not invariably—indeed, does not usually—lead to the occurrence of the complication. Moreover, as emphasized by the case of Barbero, Gray, Scott, and Kempe (9), a normal gamma globulin level is no more of a guarantee against occurrence of vaccinia gangrenosa than it is an invariably accurate indicator of antibody responsiveness.

PROGNOSIS AND TREATMENT

This is the third reported case in which a patient recovered from vaccinia gangrenosa. Crosbie and Downie (4) treated their patient with 100 ml of hyperimmune vaccinial whole blood. The patient of Barbero et al. (9) received 37 ml of hyperimmune vaccinial gamma globulin. Treatment in the present case included 10 ml of hyperimmune vaccinial gamma globulin and 1,300 ml of hyperimmune vaccinial whole blood. Recovery in this case cannot be ascribed with any certainty to treatment, as improvement began only two days after administration of the passively transferred antibody, at which time no serum neutralizing antibody could be demonstrated. In the two other nonfatal cases, improvement was noted four days after initiation of specific treatment. It is apparent, however, that the only effective therapeutic agents are hyperimmune vaccinial gamma globulin or blood. In every previous case in which only nonspecific measures, such as systemic and local antibiotics and steroids, were used, the outcome was fatal. Kempe and Benenson (24) recommend 0.6 to 1 ml/kg of hyperimmune vaccinial gamma globulin every eight to ten days until the lesions are healed.

It is of interest that of the two patients treated effectively in whom studies were performed, neither was agammaglobulinemic, and that three patients (7, 11, 13) with agammaglobulinemia who were specifically treated, died. Whether this was a matter of chance, or means a real difference in the responsiveness to therapy of agammaglobulinemic and hypogammaglobulinemic or dysgammaglobulinemic patients cannot be said at this time.

SUMMARY

The third reported case of vaccinia gangrenosa in an adult is presented. The patient was also the third to have recovered from the disease, which, when not treated with hyperimmune vaccinial gamma globulin or blood, has been uniformly fatal. The pathogenesis, etiology, prognosis, and therapy of the disease are discussed.

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SUMMARIO IN INTERLINGUA

Es presentate le tertie reporto de un caso de vaccinia gangrenose occurrente in un adulto. Iste condition, que es le plus rar e le plus serie

del complicationes de vaccination contra variola, es characterisate per un progressive extension e necrosis del sito primari del inoculation, con metastatic lesiones vaccinial e uniformemente un termination mortal si tractamento specific non es instituite.

Inter omne le casos reportate in le litteratura, septe—incluse le presente—esseva studiate conclusivemente, e in omne istos il esseva trovate que nulle responsa de anticorpore contra le virus de vaccinia occurreva. Iste manco de responsa pare esser essential in le pathogenese del infection. In le presente caso, le patiente habeva un subjacente chronic leucemia lymphatic. Le mesmo vale pro un del altere duo reportate casos in adultos. Isto es presumitemente causate per le hypogammaglobulinemia e le deprimite responsivitate anticorporee que non infrequentemente es associate con iste condition. Le altere entitate que es frequentemente presente in casos de vaccinia gangrenose es agammaglobulinemia idiopathic.

Le presente caso es le tertie reportate in que le patiente se restabliva ab le morbo. Le patiente esseva tractate con hyperimmun globulina gamma vaccinial e hyperimmun sanguine total vaccinial. Istos es apparentemente le sol efficace agentes therapeutic.

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Flavobacterium Infection as a Cause of Bacterial Endocarditis

Report of a Case, Bacteriologic Studies, and Review of the Literature

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OBSERVATION OF A FIRST CASE OF ENDOCARDITIS due to *Flavobacterium* called our attention to this microorganism which has been considered to be non-pathogenic for man. The pertinent clinical and medical bacteriological literature is therefore reviewed, and the case of bacterial endocarditis is described as an example of the pathogenicity of this organism for man, its resistance to available antibiotic therapy, and its serious prognostic significance.

The widespread use of antibiotics has gone hand in hand with a decreased incidence of bacterial endocarditis due to alpha and beta hemolytic streptococci, pneumococci, and gonococci, and an increased incidence of cases due to relatively drug-resistant organisms (1, 2) such as staphylococci, and various Gram-negative bacilli, some of which had been considered as non-pathogenic or rarely pathogenic for man.

Frequently, antibiotic therapy changes the course of bacterial endocarditis and a clear distinction between acute and subacute cases cannot always be made (1, 3, 4).

Cases of septicemia with or without bacterial endocarditis caused by Gram-negative bacilli other than *Salmonellae* or *E. coli* have been reported in the older literature (5), and more frequently recently (2, 6–11). The genitourinary tract seems to be the most common portal of entry. Cardiac surgery (11) for congenital or acquired defects, as well as intravenous catheters and cannulas (9) have recently been mentioned as other sources of infection. Most authors stress the suppressive effect of antibiotics on many of the ordinary pathogens allowing "unusual" and often highly resistant organisms to multiply and to become pathogenic.

We had the opportunity to observe a case of septicemia and fatal bacterial endocarditis, caused by an ordinarily non-pathogenic Gram-negative bacillus belonging to the genus *Flavobacterium*. No case of endocarditis due to this organism has heretofore been described, as far as we know.

CASE REPORT

Present Illness: A 66-year-old white man, operator of a fishing resort at a Southeastern Arkansas lake, was admitted to the Veterans Administration Medical Teaching Group Hospital, Memphis, Tennessee, for the first time on August 31, 1959. He complained of an episodic type of fever of three months' duration, with peaks as high as 104 F. Episodes relatively free of fever were apparently induced by several antimicrobial drugs, which he took for varying periods of time, and of which sulfisoxazole (Gantrisin) was the most effective. Upon omission of these drugs, the fever recurred. He also complained of occasional chills, lack of energy, a ten pound weight loss, and some right flank and lower back pain for the preceding three months.

Past History: He had been in good health until the onset of exertional dyspnea in 1954 and acute myocardial infarction in January, 1955, at which time suggestive evidence of calcific aortic stenosis was found. He was treated with bed rest, anticoagulants, and penicillin. In 1957 he developed prostatism with recurrent episodes of pyuria and transient urinary retention. He was catheterized but not cystoscoped. The infection responded to nitrofurantoin.

Productive cough, fever, malaise, and slight pedal edema developed in November, 1958. He was hospitalized elsewhere for ten days; pneumonia and

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possible subacute bacterial endocarditis were suspected, but could not be definitely confirmed. A systolic aortic murmur, cardiomegaly, and basal pulmonary râles were found, but splenomegaly, leukocytosis, and embolic phenomena were absent. Four blood cultures were taken which were negative. The blood urea nitrogen was slightly elevated; the urine contained 1+ protein and a few granular casts. Small doses of penicillin were started after the first blood culture. The fever subsided.

He remained relatively well until April, 1959, when he developed a pleuritic type of pain and fever. He was hospitalized elsewhere from April 4 to April 17, with the initial impression of pericarditis with effusion, as suggested by the initial electrocardiogram and X-ray findings. Nine blood cultures were negative. Subsequent electrocardiographic findings suggested coronary occlusion. Treatment consisted of anticoagulants (phenindione) and digitoxin. The fever subsided without antibiotics. Anticoagulation therapy was continued after discharge from the hospital.

On May 6, 1959, he suddenly developed gross painless hematuria, leading to hospitalization from May 7 to May 12. Bleeding stopped after discontinuance of anticoagulants, administration of vitamin K_1 oxide, and a blood transfusion. Intravenous pyelogram, cystoscopy, and retrograde urogram failed to show any abnormalities except prostatic enlargement.

Subsequently he remained free of genitourinary symptoms except for some nocturia (about three times a night). He took various antimicrobial drugs for recurrent episodes of fever, as previously described, nitroglycerin and long-acting coronary vasodilators for angina, and a digitalis preparation. He was able to do light work at his fishing resort, which included dipping out stagnant lake water from his boats.

Significant Physical Findings: On admission to the hospital, examination showed slight cyanosis and neck vein distention, cardiac enlargement with downward and lateral displacement of the apical impulse, a grade 4 systolic aortic murmur which was transmitted upward and over the entire precordium, hepatomegaly, and enlargement of the prostate.

Laboratory and X-ray Findings: The initial electrocardiogram indicated remote posterior infarction, left ventricular enlargement, and possible digitalis effect. On September 8, 1959, a right bundle branch block developed. Roentgenograms of the chest revealed cardiac enlargement which seemed to be chiefly left ventricular. The vascular shadow at the base of the heart showed slight widening on Trendelenburg position but fluoroscopy revealed normal aortic and cardiac pulsations. A calcification in the area of the aortic valve was seen on planigram at the 12 cm level.

The urine contained a trace of protein and a few white cells but showed no evidence of infection with *Flavobacterium*. Gram stain of the fresh midstream urine specimen showed a few pus cells and a few Gram-positive cocci but culture of the same specimen produced *Aerobacter aerogenes* and *Proteus morgani*. Various other organisms, predominantly enterococci, were grown from subsequent urine specimens, while Gram stains of fresh midstream urine specimens failed to show any organisms. Initial hemogram showed 6,300 white blood cells/mm^3, with 79% neutrophils, 4,200,000 red blood cells, hemoglobin, 10.9 g/100 ml, hematocrit, 37%, and a sedimentation rate of 31 mm/hour (corrected). The white blood count later rose to 13,000 with 95% neutrophils. The blood urea nitrogen was 30 mg/100 ml. The serum transaminase was 25 units on September 4, and rose to 83 units on September 6. Blood culture of August 31 showed prompt growth of a Gram-negative rod which was later identified as *Flavobacterium*. The same or-

TABLE 1. Drug Susceptibility of *Flavobacterium* "K4 Species"

Drug	Flavobacterium Isolated from Blood Culture Obtained 8/31/59 (1st Hospital Day) and 9/4/59 (5th Hospital Day)
1. *Chloramphenicol	Inhibited by 12.5 μg/ml.
2. †Erythromycin	Not sensitive to 2 or 15 μg.
3. †Kanamycin	Not sensitive to 10 or 30 μg.
4. †Neomycin	Not sensitive to 10, 30, or 60 μg.
5. †Nitrofurantoin	Not sensitive to 0.1 mg.
6. †Novobiocin	Sensitive to 5, 30, 100 μg.
7. *Oxytetracycline	Not inhibited by 100 μg/ml.
8. *Penicillin	Not inhibited by 100 units/ml.
9. *Polymixin-B	Not inhibited by 100 units/ml.
10. *Streptomycin	Inhibited by 100 μg/ml.
11. †Sulfamethoxypyridazine	Not sensitive to 0.25 μg.
12. †Tetracycline	Not sensitive to 30 μg.
13. †Triacetyl-oleandomycin	Not sensitive to 5 μg.
14. †Vancomycin	Not sensitive to 5 or 30 μg.

* Tube dilution method.
† Disc method.



FIGURE 1. Pointer indicates area of perforation.

ganism was persistently isolated from numerous subsequent blood cultures up to September 10, one day before his death. It was found to be sensitive to novobiocin in a concentration of 5 μg/ml, as tested by the disk method; it was partially inhibited by chloramphenicol, but was insensitive to all the other antibiotics, nitrofurans and sulfonamides (Table 1).

Hospital Course: Our initial impression was that this patient had arteriosclerotic heart disease with remote myocardial infarction, calcific aortic stenosis of undetermined etiology, and probably an infection of the urinary tract or bacterial endocarditis, or both. He was maintained on digitoxin. Chloramphenicol was started September 2, after a preliminary report of a Gram-positive coccus on urine Gram stain and of a Gram-negative rod in the initial blood culture. The patient continued to have several shaking chills, followed by fever up to 104 F or more, and had intermittent chest and left shoulder pain.

On September 5, identification and drug sensitivity of the first blood culture were reported. Chloramphenicol was stopped and the patient was placed on large doses of novobiocin. (Sulfisoxazole was added soon afterward, because of previous clinical response to this drug.) Septic temperatures persisted and a pericardial rub was heard on one occasion. Sudden dyspnea, hiccoughs, nausea, apprehension, and a temperature drop from 102 to 98 F developed on the evening of September 10, without evidence of shock or any new auscultatory findings. He seemed improved but the next morning he developed substernal and left arm pain, a drop in blood pressure, a rapid and irregular pulse, and electrocardiographic findings of supraventricular tachycardia with wandering pacemaker and marked subendocardial ischemia. Right bundle branch block (first seen September 8) persisted. He improved on intravenous infusions of dextrose in water with added potassium chloride and norepinephrine. A later electrocardiogram on the evening of September 11 showed a regular sinus tachycardia with right bundle branch block and subendocardial ischemia. At 10 PM he suddenly developed pulmonary edema and died.

Necropsy: Both pleural cavities contained about 500 ml of straw-colored fluid. There were bilateral, firm, apical, pleural adhesions. The pericardial cavity was completely obliterated by old fibrous adhesions. The left lung weighed 440 g and the right lung, 700. There was evidence of pulmonary edema, but not of pulmonary emboli, infarcts, pneumonia or bronchial obstruction. The heart weighed 540 g and showed numerous petechiae on its roughened epicardial surface. The aortic valve was calcified. A friable vegetation was attached to the ventricular surface of the anterior cusp, near the base of the valve which was ruptured at this point (Figure 1). The vegetation extended onto the underlying myocardium which was ulcerated at this spot. The mitral valve was somewhat thickened and opaque, and the chordae tendineae were shortened and thickened. The left ventricle measured 1.6 cm and the right, 0.4 in thickness. The posterior portion of the septum and of the left ventricle showed extensive scarring with an area of thinning in the septum. The coronary arteries and the entire aorta showed marked atherosclerotic changes, but the coronary ostia and vessels were

patent. The spleen was large and soft, showed thinning of the capsule, and was adherent to the diaphragm.

The liver was enlarged and showed passive congestion. The kidneys were of normal size and showed a finely granular surface with irregular thinning of the cortex. The excretory system was not remarkable and the urine in the bladder appeared to be clear. The prostate was slightly enlarged, firm, and nodular. The gastrointestinal tract was not remarkable. The brain showed moderate sclerosis of the circle of Willis but no abnormalities on serial section.

Microscopic Examination: Sections of the aortic valve showed thickening and calcification of the leaflets. Polymorphonuclear cell infiltration extended from the base of the valve into the adjoining necrotic myocardium. Another section showed a small mycotic aneurysm of the aortic valve with rupture into the myocardium and an acute myocardial abscess. A small antemortem thrombus was found in a peripheral vessel of the lung. The myocardium of the left ventricle showed hypertrophy and extensive fibrosis.

The kidneys showed areas of focal scarring and interstitial lymphocytic and plasma cell infiltration. Occasional glomeruli were hyalinized and the small and medium sized renal vessels showed moderate sclerotic changes.

Smears obtained from the vegetation and myocardial abscess showed many Gram-negative bacilli which proved to be flavobacteria on culture. Smears from the spleen showed many pus cells without any organisms, but culture of this material showed *Flavobacterium*.

Bacteriological Studies

METHODS

Incubation of cultures was performed at 37 C unless otherwise stated. For hemolysis studies, human bank blood was employed. Fermentation studies were done by adding 1% fermentable substances to nutrient broth containing brom cresol purple as an indicator. Tubes were observed for at least three weeks. The Ehrlich-Boehme technique was employed in testing for indol. The methyl-red and the Voges-Proskauer tests were performed with the use of Difco-M.R.-V.P. medium. Thiogel after the formula of the Baltimore Biological Laboratory was used to determine liquefaction of gelatin; this medium was incubated at 37 C, then chilled in the refrigerator for the final reading. In order to determine the production of hydrogen-sulfide, Difco triple sugar iron agar was used as well as lead-acetate strips placed above nutrient agar slants and above brain heart infusion containing 0.1% agar. For urease production, Difco urea agar base was employed. Catalase production was determined by removing a small portion of growth from a nutrient agar slant and mixing this on a glass slide with some 30% hydrogen peroxide. Difco nitrate broth was used for nitrate reduction studies. For motility studies, direct microscopic studies of broth cultures a few hours old were made; Difco motility medium and thiogel medium were also employed for this purpose.

RESULTS

The organism recovered in this case is a motile, Gram-negative rod. Spores have not been observed. Colonies produced on blood agar plates grow to a diameter of 1 mm in 24

Table 2. Biochemical Reactions of *Flavobacterium* sp. K4

Monosaccharides	dextrose	+ (weak)	indol	−
	xylose	−		
	rhamnose	−	Voges-Proskauer	−
Disaccharides	lactose	−	methyl red	−
	maltose	−		
	saccharose	−	gelatin	−
Polysaccharides	starch	−	hydrogen sulfide	−
	inulin	−		
	glycogen	−	urease	+
Alcohols	mannitol	−	catalase	+
	dulcitol	−		
	adonitol	−	nitrate reduction	+
	sorbitol	−		
Glucosides	salicin	−	citrate	+

hours. They are smooth, round, raised, greyish-white in appearance, mucoid, and have an entire edge. The colonies are non-hemolytic.

The organism is a facultative anaerobe. It grows well on plain agar. It also grows well at room temperature. The organism is quite inactive biochemically as is shown in Table 2. It attacks dextrose very weakly with the production of a small amount of acid but this reaction usually reverts back to alkaline in a few days. Other monosaccharides, disaccharides, polysaccharides, alcohols, and glucosides were not attacked, as shown in Table 2. Other tests to which this organism is negative are the following: indol, Voges-Proskauer, methyl red, gelatin, and hydrogen sulfide. Positive reactions are produced in the following tests: urease production, catalase production, reduction of nitrates to nitrites, and utilization of citrate. When grown in litmus milk, there is no coagulation. The milk, however, is slowly digested from the top of the tube down and there is a reduction of the color of the litmus in the digested portion.

The pigment produced by the organism was pale in color and varied from pale buff to yellowish-tan to lemon color. The strongest color production occurred when we used triple sugar iron agar. On nutrient agar, the pigment sometimes did not appear until after several days of incubation. Colonies on blood agar appeared to be greyish-white but when some of the growth was scraped off with a wire loop and viewed in this manner, it was seen to have pigment. No pigment was produced in any of the liquid media used. On agar media, there was no diffusion of pigment through the agar.

One interesting observation made in the study of this organism was that the motility was negative as observed by the use of the two motility media. However, by direct microscopic examination, it was definitely shown that the organism was motile. This was repeated several times in order to rule out motion due to flowing media and to rule out Brownian motion.

Lots of five 25 g and five 15 g mice, and two male guinea pigs, inoculated intraperitoneally with 0.5 or 1 ml of a cloudy suspension, respectively, showed no infection due to *Flavobacterium*. Two large rabbits, each inoculated by both the subcutaneous and intraperitoneal routes with 1 ml of the suspension, failed to evidence infection.

CLASSIFICATION OF THE ORGANISM

The organism isolated in this case meets the requirements for assigning it to the family of *Achromobacteriaceae* as described in *Bergey's Manual of Determinative Bacteriology* (12). Members of this family may produce a non-diffusable pigment ranging from grey to brown, yellow, or orange. They are further characterized by lack of power or by feeble power in attacking carbohydrates. They generally do not produce enough acid to curdle milk.

Of the three genera of the family *Achromobacteriaceae* it is most logical that the organism in question be assigned to the genus *Flavobacterium*. This conclusion was arrived at after a thorough comparison of its characteristics with those of the three genera of Flavobacteria described in *Bergey's Manual of Determinative Bacteriology*.

Of the genus *Flavobacterium* there are 27 different species listed in *Bergey's Manual of Determinative Bacteriology*. Most of these species are inadequately described according to present day standards.

It has not been possible to identify the strain isolated in this case with any of the 27 species of Flavobacteria listed in *Bergey's Manual of Determinative Bacteriology*.

The serologically similar group of four strains of Flavobacteria which were isolated from four cases of neonatal meningitis by Van-

TABLE 3. Important Bacteriological Characteristics

	F. meningosepticum	*Flavobacterium* sp K4
Motility	−	+
Reduction of nitrates	−	+
Indol production	+	−
Carbohydrates, late fermentation	+	−
Gelatin liquefaction	+	−

depitte, Beekmans, and Buttiaux (13) in the Congo were not thoroughly characterized. A detailed bacteriological study was to follow but this report has not yet been seen. However, from consideration of the few characters enumerated, it is very unlikely that they were dealing with the same species that is the object of the present study.

King (14) has made a very careful examination of a group of Flavobacteria associated with meningitis in children. The organisms in this group were bacteriologically similar. For this group of organisms, she has suggested the name *Flavobacterium meningosepticum*. The organism described in this paper, which for convenience is designated now as *Flavobacterium* sp K4 has been compared with *Flavobacterium meningosepticum* and it is clear that they cannot be identified as one and the same. This lack of identity may be more clearly shown by their important bacteriological characteristics, as listed in Table 3.

The organism isolated in the case described in this paper has been designated as *Flavobacterium* sp K4. Although it has not been possible to identify it with any other species previously described, it seems unwise at the present time to attempt to assign it a more specific name. Where only one isolation is under consideration, it must be borne in mind that variations from a normal behavior may account for its individuality.

Flavobacterium sp K4 has been deposited with the American Type Culture Collection.

Discussion

We are dealing here with a case of bacterial endocarditis due to a Gram-negative bacillus of the genus *Flavobacterium*, superimposed on calcific aortic stenosis of undetermined but presumably rheumatic etiology. Death resulted from rupture of a mycotic aneurysm of an aortic valve cusp, with acute left ventricular failure and pulmonary edema. Myocardial necrosis and abscess formation were probably responsible for the associated rhythm and conduction disturbances. Contributory factors were coronary atherosclerosis with remote myocardial infarction and scarring.

Flavobacteria are mostly found in water of lakes, ponds, streams, rivers, the sea, and in the soil. They are Gram-negative rods, motile or non-motile, which produce yellow, orange, red, or brown pigments; they do not produce gas, and they are aerobic or facultative-anaerobic. Some authors include them among the chromobacteria (15).

According to Schaub and Foley (16), "A number of Gram-negative bacilli with variable characteristics are frequently isolated from various types of clinical material. These organisms are diffcult or impossible to identify specifically.... Many of these strains produce a yellow pigment on solid media and may be regarded as *Flavobacterium*. The non-pigmented strains may be *Achromobacter*. These organisms are not pathogenic, their usual source is water and they can be regarded as contaminants."

Despite this opinion, some flavobacteria may occasionally be pathogenic, although references in the literature are few.

In 1929 Pangalos (17) recovered a motile Gram-negative bacillus (*"Bacillus rubro-luteus"*), which produced yellow pigment, from the blood stream of a woman with non-fatal septicemia following curettage. It is not quite certain whether this organism can be classified as a flavobacterium.

Sherwood (18), in 1931, isolated a flavobacterium from the spinal fluid of a case of meningitis. He described its bacteriologic characteristics and found it to be pathogenic in guinea pigs and rabbits. Acute orchitis and focal lesions in the lungs, liver, and spleen of these animals developed after intravenous inoculation. The organism was named *Flavobacterium orchitidis*. Bozzo and Pino (19) described a case of mixed meningitis due to *Alcaligenes faecalis* and *Flavobacterium arborescens* in a 13-year-old Sardinian boy who recovered after treatment with sulfonamides, streptomycin, and penicillin, in spite of a low *in vitro* sensitivity to these drugs.

Brody, Moore, and King (20) reported on two outbreaks of meningitis, which affected primarily premature infants in hospital nurseries and were caused by a Gram-negative bacillus. This bacillus was later definitely identified by King (14) who described its biochemical and serologic characteristics. She named this organism *Flavobacterium meningosepticum*. One of the cases occurred in an adult. The cases were collected from a number of states, mostly in the Southeastern United States. Vandepitte et

al. (13) reported four cases of neonatal meningitis caused by *Flavobacterium* in a hospital at Luluabourg in the Congo.

Recently Kleeman, Hewitt, and Guze (21), in their monograph on pyelonephritis, mentioned an outbreak of 100 cases of urinary infection due to *Flavobacterium* observed by Hallman, Hewitt, and Finegold during a ten-month period. These cases occurred after cytoscopy or transurethral procedures. Bacteremia occurred on two occasions. The organism was sensitive to sulfonamides and to 10 μg per ml of novobiocin, but was resistant to other antibiotics.

The source and portal of entry of the infection in our patient are not definitely known, but frequent and prolonged urinary infections and contact with infected water both occurred and need to be considered.

Many authors implicate genitourinary tract disease as the most frequent source of Gram-negative bacillemia. Urinary tract instrumentation often precedes the development of such urinary infections. Our patient gave a history of prostatism with recurrent urinary tract infections and genitourinary tract instrumentation. Microscopic examination of his kidneys showed some chronic inflammatory parenchymal changes in addition to vascular nephropathy. However urine cultures before his death did not show *Flavobacterium,* and post-mortem cultures were not obtained from the genitourinary tract. This does not necessarily rule out the genitourinary tract as the source of infection since it is well known that the bacterial flora in chronic pyelonephritis may frequently change, especially when the patient is subjected to various antimicrobial drugs. The concentration of antimicrobial drugs in the urine may be sufficient to eradicate the organisms or at least to inhibit their growth, whereas the concentration of these drugs in the blood is not high enough to sterilize the blood stream and especially not to kill all the bacteria in the endocardial vegetations.

The reported occurrence of flavobacteria in water in the external environment led us to postulate that lake water or water in boats where the patient worked might have been the source of the organism. However, numerous cultures of water from the lake in question and of water in unused boats showed no evidence of flavobacteria similar to those found in the patient's blood stream.

Summary

A case is reported of fatal endocarditis and septicemia due to *Flavobacterium,* including a study of the organism involved. The increased incidence of "unusual" Gram-negative bacillary infections is discussed. Some of these microorganisms, including *Flavobacterium,* have rarely or never before been found pathogenic for man. To our knowledge, this is the first reported case of endocarditis due to *Flavobacterium*. The increased use of antibiotics is thought to be the main cause of the greater incidence of previously uncommon infections. This strain of *Flavobacterium* was found to be resistant to most of the common antibiotics, as were most of the Gram-negative microorganisms causing septicemias reported by others. The role of the genitourinary tract as a possible portal of entry is described.

Summario in Interlingua

Le extense uso de antibioticos ha coincidite con un plus alte incidentia de endocarditis causate per inusual e frequentemente resistentissime organismos gram-negative, incluse multes que previemente esseva considerate como non-pathogene o rarmente pathogene pro le homine. *Flavobacterium* pertine a iste categoria. Iste genere include numerose species de pigmentogenic bacillos de aqua e humus le quales es generalmente considerate como saprophytos. Il existe rar reportos de infection flavobacterial in humanos, in le majoritate del quales il se tractava de meningitis neonatal. In tanto que nos lo sape, nulle caso de endocarditis flavobacterial ha previemente essite describite. Il esseva nostre privilegio observar un tal caso.

Un masculo de 66 annos de etate esseva hospitalisate a causa de un prolongate febre que esseva domate incompletemente per plure intermittente cursos de therapia antimicrobial. Le anamnese includeva un infarcimento myocardial, constatationes suggerente le presentia de calcific stenosis aortic, prostatismo con recurrente episodios de pyuria, retention urinari, e instrumentation in le vias urinari. Al occasion hic reportate ille presentava le tableau de septicemia e endocarditis probabile. Plure culturas de sanguine monstrava un rapide crescentia de flavobacterios que esseva sensibile a novobiocina e levemente sensibile a chloramphenicol.

In despecto de un vigorose tractamento con le mentionate e altere antibioticos e de therapia cardiac e supportative, le patiente moriva intra 11 dies. Le necropsia revelava hypertrophia e cicatrisation cardiac, vegetationes attachate al calcificate valvula aortic, ruptura de un aneurysmo mycotic de un cuspide aortic, e un abscesso myocardial. Le renes monstrava alterationes sclerotic e infiltration interstitial de cellulas ronde. *Flavobacterium* esseva isolate ab le vegetationes, le abscesso myocardial, e le splen.

Le organismo culturate ab le circulation de sanguine e ab le specimens necroptic esseva definitemente identificate como un flavobacterio. Illo differeva in certe respectos del previemente describite species de iste genere e esseva tentativemente designate como *Flavobacterium sp. K1*. Su characteristicas biochimic e altere es reportate in detalio.

Infectiones e instrumentation del vias genito-urinari es le fontes le plus commun de septicemias gram-negative. Le facto que *Flavobacterium* non esseva isolate ab le urina del presente patiente non exclude iste possibilitate, proque le antecedente chimotherapia pote haber eliminate le organismo ab su vias genito-urinari sed non ab le vegetationes cardiac.

Iste caso es reportate pro sublinear de novo le crescente importantia de inusual organismos gram-negative como agentes etiologic de septicemias e de endocarditis bacterial. *Flavobacterium* debe esser addite al semper-crescente lista del pathogenos potential in iste area.

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CLINICAL STAFF CONFERENCE

Ecology of a Newly Recognized Common Respiratory Agent RS-Virus

Combined Clinical Staff Conference at the National Institutes of Health

Moderator: VERNON KNIGHT, M.D., F.A.C.P.

Discussants: ALBERT Z. KAPIKIAN, M.D., HOWARD M. KRAVETZ, M.D., ROBERT M. CHANOCK, M.D., J. A. MORRIS, PH.D., ROBERT J. HUEBNER, M.D., JOSEPH E. SMADEL, M.D., and HUGH E. EVANS, M.D.

Bethesda, Maryland

DR. VERNON KNIGHT: Participants in our program today will describe current research on the common cold and one agent, the respiratory syncytial virus, in particular. Volunteers for exposure to this virus came from Federal prisons in the area, and much of the credit for the success of the project to date goes to Mr. James Bennett, Director of Federal Prisons, and to Dr. Harold Janney, chief physician for the prison system, who have given us excellent cooperation.

Studies with volunteers are not new and usually they are conducted within penal institutions. But it seemed to us that more precise, useful information could be gained by bringing the prisoners to the Clinical Center where our laboratory facilities are located. I think our experiments will demonstrate that we have been able to make detailed observations of these volunteers which would have been difficult had it been necessary for us to go to the prisons.

Our first speaker is Dr. Albert Kapikian of the Laboratory of Infectious Diseases, who will describe the natural history of the respiratory syncytial virus infection in children as a preliminary to our own experiments.

DR. ALBERT Z. KAPIKIAN: I shall present briefly our experience with an outbreak of pneumonia which was associated significantly with respiratory syncytial virus infection in a population of 90 infants and children. A complete report of this outbreak appears elsewhere (1). This population, six to 50 months of age, was located at Junior Village, a welfare institution in the District of Columbia for homeless, normal children. This study group has been under the clinical surveillance of the Laboratory of Infectious Diseases, with a full-time pediatrician and medical staff in attendance.

At the start of the outbreak, 65 of the study group resided in Eisenhower Cottage and 25 in the Infirmary. The Infirmary, located about 300 yards from Eisenhower Cottage, housed the

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TABLE 1. Incidence of Pneumonia and Serologic Evidence of Respiratory Syncytial Virus (RS) Infection in Infirmary and Cottage Populations (1)

Location	Mean Age (Months)	Number at Risk	Pneumonia		Serologic Evidence of RS Infection		
					Number Tested	Neut. and/or CF Antibody Rise (≥ Fourfold)	
			No.	%		No.	%
Infirmary	17	25	20	80	23	21	91
Cottage	29	65	16	25	57	52	91
Total	26	90	36	40	80	73	91

acutely ill during periods of illness. In addition, on account of overcrowding in the Cottage, the Infirmary provided permanent residence for those who were in need of greater individual attention because of infancy and not infrequently because of psychological need, malnutrition, or debilitation.

Except for occasional outbreaks, pneumonias have occurred in the study group at the rate of three to five cases a month. However, as is shown in Table 1, in a four week period from April 24 to May 21, 1960, 36 (or 40%) of the 90 residents developed pneumonia. It is seen that 20 (or 80%) of the Infirmary children and 16 (or 25%) of the Cottage children developed pneumonia. In addition, 91% of each group showed serologic evidence of infection with RS virus in tests with their pre-outbreak and post-outbreak sera.

Table 2 shows the distribution of pneumonia and other febrile illnesses of 100.6 F or greater in both Infirmary and Cottage during the four week period. Although the mean age of the Infirmary residents was lower than that of the Cottage, it did not appear that this could explain the striking difference in the incidence of pneumonia at each location, since 13 of 14 Infirmary children and only one of 18 Cottage children between 12 and 23 months of age developed pneumonia. One of several possible explanations for this difference may be that the Infirmary residents were more susceptible to developing the severe illness, pneumonia, because they were, in general, a less robust group than that of the Cottage. Table 2 also shows that there were many other febrile illnesses during the four week period as only six of the 90 children did not develop a febrile illness of 100.6 F (R) or greater.

Figure 1 presents the pneumonia outbreak as it occurred by day in both the Cottage and Infirmary. The day of onset for pneumonia was considered to be that day when the rectal temperature first reached 100.6 F or greater. In the Cottage the onset of the first case occurred on April 24, and we notice that the second and third cases occurred on April 28, four days later. It is of interest that this case of April 24

TABLE 2. Age Distribution of Pneumonia and Other Febrile Illnesses in Infirmary and Cottage, April 24, 1960 to May 21, 1960 (1)

Age (Months)	Infirmary					Cottage				
		Pneumonia		Febrile Illness (≥ 100.6) other than Pneumonia			Pneumonia		Febrile Illness (≥ 100.6) other than Pneumonia	
	No.	No.	%	No.	%	No.	No.	%	No.	%
8–11	6	5	83	1	17	—	—	—	—	—
12–23	14	13	93	1	7	18	1	6	17	94
24–35	4	2	50	2	50	33	11	33	19	58
36–50	1	0	—	1	100	14	4	29	7	50
Total	25	20	80	5	20	65	16	25	43	66

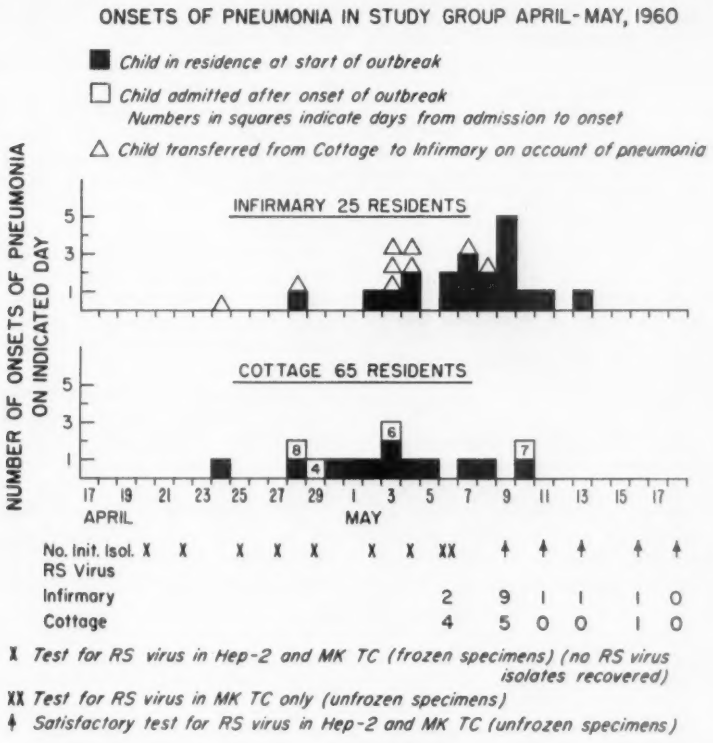


FIGURE 1. Onset of pneumonia in study group April to May 1960 (1).

was transferred to the Infirmary on the same day, April 24, and the first case in a permanent Infirmary resident had its onset four days later, on April 28, with the second case occurring on May 2—again an interval of four days. In addition, one child had the onset of pneumonia four days after admission to the Cottage. These data would indicate that the incubation period for the pneumonia illness was four days.

Figure 1 also shows the day when RS virus was first isolated from each of 24 children. RS virus was not isolated before May 6 when the throat swab specimens were frozen and thawed before inoculation, a procedure which probably caused the inactivation of the labile RS virus. On May 6 when fresh specimens were inoculated into monkey kidney tissue culture alone [the Hep-2 (human epithelial) tissue was contaminated], six isolations of RS virus were made. On the May 9 day of testing, 14 initial RS virus isolations were recovered from fresh specimens in Hep-2 culture. In this study, when both monkey kidney and Hep-2 were used, monkey kidney was less than one-third as sensitive as Hep-2 culture for the isolation of RS virus.

By cross-sectional analysis the test for association of RS virus with illness was based on isolations made on May 9, the first day of adequate testing and the day when 16 isolations (14 initial and two shed) were made. To determine if RS virus was associated with illness, the illness attack rate during the five day period bracketing virus isolations (test period) among children who were RS virus positive on May 9 was compared with the attack rate during the same five day period among children who were RS virus negative on May 9 (cross-sectional analysis). The five day period was chosen on the assumption that if the virus caused the illness, then the onset of the febrile episode should occur up to three days before, the day of, or the day after virus isolation, i.e., on May 6, 7, 8, 9, or 10 with May 9 as the day of virus isolation. The adequacy of the five day period was supported by the volunteer studies which

TABLE 3. Respiratory Syncytial (RS) Virus Isolations and Onset of Febrile Pneumonia at Junior Village (1)

May 9 Test Day	Onset of Febrile Pneumonia*			Per Cent Pneumonia
	Yes	No	Total	
Virus isolated	10	6†	16	63
Virus not isolated	5	60†	65	8
Total	15	66	81	19

* Onset of febrile pneumonia (100.6 F or greater) occurred three days before, day of, or day after May 9 (May 6, 7, 8, 9, 10).

† One individual in each group developed pneumonia with maximal temperature of 100.4 F.

($P < .0001$ Yates).

will be discussed later. Using this cross-sectional analysis we first studied the data for association of RS virus infection and the most objective measure of illness, i.e., a febrile episode of 100.6 F or greater. In the Cottage no association could be shown. However, in the Infirmary a significant association was found, as eight of ten patients with RS virus isolations and only four of 13 who were virus negative developed a febrile episode within the five day test period ($P < .05$ exact test).

A similar cross-sectional type of analysis was made to determine if the RS virus isolations of May 9 were significantly associated with the onset of a febrile pneumonia. Table 3 shows that within the five day test period, May 6, 7, 8, 9, and 10, ten (63%) of 16 patients with RS virus isolations on May 9, and only five (8%) of 65 patients who were RS virus negative on May 9 developed febrile pneumonia. This difference in the occurrence of pneumonia in the virus-isolated and virus-not-isolated groups is statistically significant ($P < .0001$ Yates), indicating an association between RS virus isolation and the onset of a febrile pneumonia illness. Incidentally, similar analysis limited to either Infirmary or Cottage groups alone showed a significant association also ($P < .05$ exact test).

The cross-sectional analysis did not adjust for attributes such as age, sex, race, duration of residence, duration of illness, etc., some of which might influence occurrence of illness.

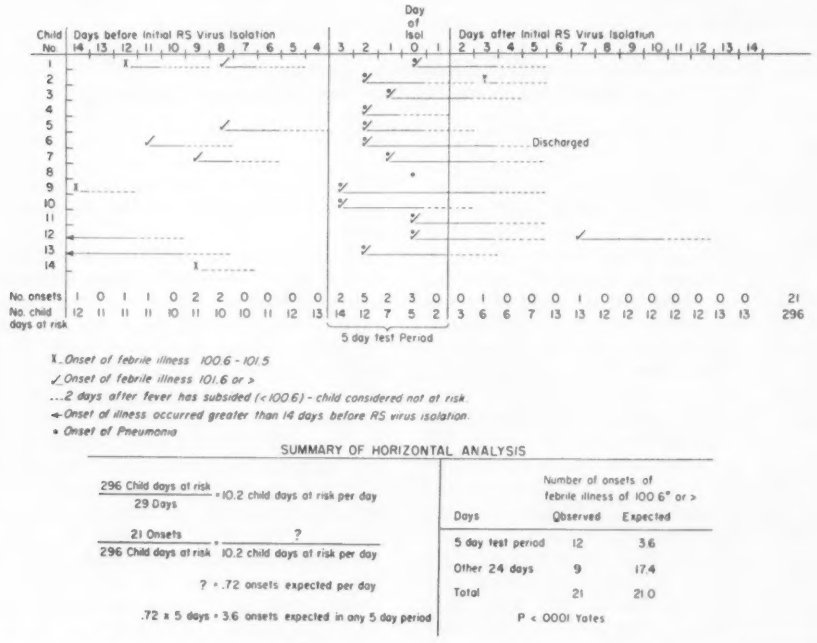


FIGURE 2. Febrile illness experience of 14 children in infirmary with RS virus isolations at time of initial isolation as compared with that of the same children immediately before and after this time (1).

TABLE 4. Clinical Findings in 16 Patients with Pneumonia and Associated RS Virus Isolation and 20 with Pneumonia and No Associated RS Virus Isolation (1)

Initial Symptom	Virus Isolated		Maximal Temperature (R)	Virus Isolated		Duration of Fever 100.6 or >	Virus Isolated	
	Yes*	Not†		Yes*	Not†		Yes*	Not†
	No. of Cases (Tot. 16)	No. of Cases (Tot. 20)		No. of Cases (Tot. 16)	No. of Cases (Tot. 20)	Days	No. of Cases (Tot. 16)	No. of Cases (Tot. 20)
Fever 100.4 or >	16	20	100.4	1	1	1–2	4	6
100.6 or >	15	19	100.6–101.8	3	2	3–4	9	5
Coryza	8	11	102. –102.8	2	4	5–6	2	4
Otitis	1	2	103. –103.8	4	11	7–8	0	3
Cough	2	4	104. –104.8	6	1	9– >	1	2
			105 or >	0	1			
Symptoms and signs during illness								
Coryza	14	18						
Cough	15	18						
Tympanic membrane erythema	7‡	6§						
Pharyngeal erythema	5‖	4#						
Râles, and/or decreased breath sounds	16	20						

* Onset of pneumonia three days before, day of, or day after initial virus isolation.
† All had four-fold or greater rise in CF and/or NAB to RS virus except one who had only two-fold CF rise; two had RS virus isolations but four days before onset of pneumonia.
‡ Only 13 patients examined.
§ Only 15 patients examined.
‖ Only 11 patients examined.
Only 16 patients examined.

Therefore a horizontal analysis was made comparing the febrile illness experiences of those children from whom RS virus was isolated with the febrile experiences of the same children two weeks before and two weeks after a five day period (test period) bracketing initial virus isolation (horizontal analysis). Figure 2 shows that during the test period the 14 Infirmary children who were RS virus positive experienced the onset of 3.3 times the expected number of febrile illnesses ($P < .0001$ Yates) indicating a striking association between RS virus infection and onset of febrile illness in these children. In a similar analysis of the ten RS virus positive Cottage children, no association could be found.

Table 4 summarizes the clinical findings in the 36 patients with pneumonia. Among the 16 patients with pneumonia and an associated RS virus isolation we see that, as an initial symptom, 15 (94%) had fever of 100.6 F or greater, while eight had coryza and two had cough. The significant findings during illness were coryza in 14 (88%); cough in 15 (94%); erythema of the tympanic membrane in seven of 13; erythema of the pharynx in five of 11; and moist crepitant inspiratory râles, decreased breath sounds in all 16, or both. The râles occurred in circumscribed patchy areas most frequently at the lung bases posteriorly but occasionally both anteriorly and posteriorly, or anteriorly alone. They were both unilateral and bilateral in distribution. It is of interest that the râles appeared before the onset of fever in several cases and occasionally persisted three to four days after the temperature had returned to normal levels. The average maximal temperature (R) was 103 F and the average duration of fever of 100.6 F or greater was four days. The ranges and duration are shown in Table 4.

The distribution of findings in the other 20 patients with pneumonia and no associated RS virus recovery was similar to those with pneumonia and associated RS virus isolations, suggesting that they were also associated with RS virus infection.

In summary, we have described a fairly sharp outbreak of pneumonia which was significantly associated with RS virus infection— an association which would indicate an etiologic relationship.

DR. VERNON KNIGHT: Dr. Howard M. Kravetz, Laboratory of Clinical Investigations, will describe the disease which we observed on our wards as it occurred in normal adult volunteers.

DR. HOWARD M. KRAVETZ: Dr. Kapikian has described the salient features of dis-

TABLE 5. Signs and Symptoms of a Typical "RS Cold"

	Per Cent
Nasal discharge	100
Nasal obstruction	100
Sneezing	100
Nasal erythema	83
Malaise	83
Pharyngitis (minimal)	83
Headache	72
Cough	61
Anorexia	50
Chest pain	39
Eye pain	33
Generalized myalgias	28
*No patient had fever	

ease caused by the respiratory syncytial virus in children. Our clinical volunteer study was designed to yield a correspondingly clear picture of this infection in an adult population. A complete report of this work appears elsewhere (2).

The 46 male volunteers were divided into three groups of 15 or 16 men, each of which was studied for a two to three week period. They were selected on the basis of age (21 to 35 years) and the presence of a demonstrable level of antibody to the respiratory syncytial virus. Each man was examined 24 hours before being admitted to the Clinical Center in order to rule out any active infection in the respiratory tract.

At the Clinical Center the men were divided again, on the basis of varying levels of antibody, into several groups. Then by a random method three men were placed in a room. A period of strict isolation was then begun, which lasted from seven to 12 days. During this period of time no volunteer was allowed to leave his room. Only four physicians, comprising a morning and afternoon examining team, were permitted access to the room. Each physician before entering the room had to don a gown and mask and these were changed between each group of patients.

All nursing, housekeeping, and kitchen staff were denied direct contact with the volunteer group. The purpose of this type of quarantine was to prevent the entrance of another infectious agent into the study population, and to prevent the control group from being infected with the respiratory syncytial virus.

The success of this type of strict isolation is reflected by the fact that no one on the staff, no one in the control group, and no patient who was on the ward at the time of these experiments had a clinical infection, or recovery of the respiratory syncytial virus from his nasopharynx.

Once the men had passed through an additional 72 hours of quarantine they were given a 1.5 milliliter inoculum of either virus or sterile tissue culture fluid by a physician not on the examining team. In no room was both control and infectious material inoculated. The double blind technique was utilized throughout all experiments.

The men were then observed for the beginning of illness due to this infectious agent. Initially a set of criteria were formulated in order to judge the type and extent of illness. This was based upon past experience with volunteer studies done in the United States and England with the common cold.

A color chart (3), in addition to careful physical examination, was employed in the first experiment in order to judge the changes in the mucous membranes of the nasopharynx in the infected and uninfected state. This, plus examination of the lungs, was done twice daily to detect any evidence of upper respiratory tract disease. It soon became quite evident that the condition of the nasopharynx varied from day to day, and even from hour to hour in the same individual. Evaluation of the illness caused by the RS virus was then judged by the combination of changes in the nasopharynx plus the various signs and symptoms presented by each volunteer. These were judged as to subjective severity as noted by the volunteer, and objectively

by the combined opinion of both observing teams of physicians.

We have summarized in descending order of occurrence the signs and symptoms of an "RS cold" in Table 5. Each of the 18 men who had clinical illness, of a total of 35 patients receiving virus, had nasal discharge, nasal obstruction, and sneezing. Immediately this puts this disease, as contrasted to Dr. Kapikian's group of children, into the category of a common cold. We see that in over 60% of our patients there was a nonproductive cough; in 70%, a mild headache; and in over 80%, pharyngitis, which was minimal, and malaise, which was rather profound, lasting two to three days.

The remainder of this table includes those features often associated with the common cold, with perhaps the exception of chest pain, which was transitory and mild. It is of note, as contrasted to the children, that no patient in our group had fever at any time.

Now one might say this is a very subjective way to look at a common cold, and we indeed thought that there was another clinical approach to this problem that was more objective. This was done by quantitating the total daily amount of nasal secretion throughout the entire period of hospitalization as noted in Table 6, which demonstrates the maximal nasal secretion of each patient. It is divided into three patient groups: those receiving the virus and having clinical illness; those receiving the virus and not having clinical illness; and those receiving control fluid.

TABLE 6. Day and Amount of *Maximal* Nasal Secretion Post Inoculation.

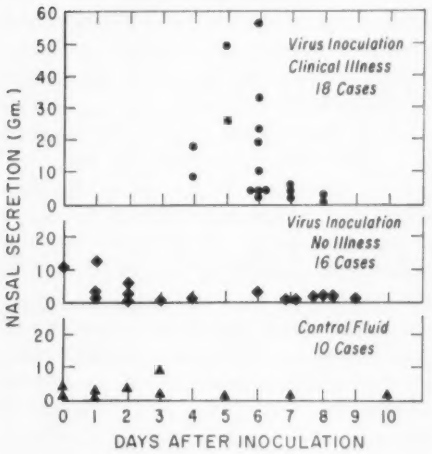
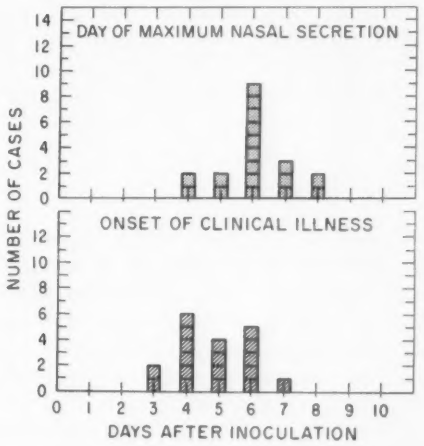


TABLE 7. Incubation Period of "RS Cold" Tabulated by Day of Maximal Nasal Secretion and Onset of Signs and Symptoms



In the first group, nine of 18 patients who had clinical illness produced large amounts of nasal secretion with a maximal value for one patient of 59 grams of material in one 24-hour period. The major grouping of nine patients occurs on day six, which is in the middle of the period of observed clinical illness. The other members of this group are grouped together from day four to day seven with the exception of two patients, and this again fits in with the pattern of clinical illness lasting from four to seven days.

The remaining two groups show low levels of maximal nasal secretion and no precise grouping on any particular day.

In Table 7 we have plotted the day of maximal nasal secretion and the number of cases of clinical illness. This incubation

TABLE 8. Range of Duration of Illness

No. of Cases	Duration of Illness	Per Cent
1	2	6
2	3	11
5	4	28
3	5	17
3	6	17
4	7	22

period of this particular illness induced in volunteers judging by the day of maximal nasal secretion, is four days, but considering the illness from the onset of signs and symptoms it is three days. This corresponds with the incubation period of this illness in children of three to four days.

In Table 8 the duration of illness of all of the 18 clinical cases is tabulated. In over 60% of this group the duration of illness was four to seven days, again corresponding to the experience in children.

In summary, we have studied a group of normal adult volunteers infected under controlled conditions with respiratory syncytial virus. A definite clinical illness with an incubation period of three to four days and having a duration of four to seven days was found in over 50% of those patients receiving an inoculation of virus.

This illness was characterized in the adult by coryza and an afebrile course, as contrasted to pneumonia and a febrile course in children.

DR. VERNON KNIGHT: The next portion of our discussion will concern the virological data of this volunteer study. Dr. J. A. Morris, Laboratory of Virology and Rickettsiology, Division of Biologics Standards, will describe the studies which he made, assisted by Mr. C. G. Aulisio, and explain the reasons for conducting such studies.

DR. J. A. MORRIS: Latent agents of infectious diseases in laboratory animals and in cell cultures are frequently encountered in experimental procedures. Their occurrence is of importance since they might account, first, for errors in interpretation of test results and, second, for trouble in screening test materials for their presence. The current concern of the Division of Biologics Standards in latent viruses is the determination of the part played by presence of these agents in host cell systems employed in the preparation of biologics for use in man.

Tissues of the rhesus monkey are an especially rich source of latent viruses. To the 50 or so such viruses recovered from tissues and excreta of the rhesus, another was added recently. Presence of the new virus in rhesus kidney cell cultures was first detected when Sweet and Hilleman (4) inoculated rhesus kidney cell culture material into kidney cell cultures of the African green or grivet monkey. In the susceptible grivet cell system the new agent induces formation of progressive vacuolation of the cultured cells which leads ultimately to almost complete cellular degeneration. The agent, tentatively called vacuolating virus (SV_{40}), differs in a number of properties from any of the viruses previously described and has been detected as a contaminant in many virus seed stocks as well as in living virus vaccines prepared in cultures of rhesus kidney cells. Sweet and Hilleman concluded that the vacuolating virus appears to be a common and essentially ubiquitous contaminant of rhesus cell cultures, but occurs less frequently in cynomologus and rarely in the African green monkey. Thus, this agent becomes of considerable importance to the Division of Biologics Standards which must insure the absence of extraneous agents in live vaccines prepared in monkey cell cultures. The interest of our laboratory in the vacuolating virus is focused on its potentialities as an infectious or pathogenic agent for man. Information on this point must be obtained before it can be decided whether the vacuolating virus is mainly a nuisance, a potential hazard, or a definite

hazard when present in live viral vaccines used for immunization purposes.

Our studies of the vacuolating virus have been directed toward detection of its presence in materials prepared for use in human volunteer work, elimination of the virus in inocula destined for human and animal use, and determination of the serologic response in man to nasopharyngeal instillation of the agent. In the studies reported here, Dr. Karl M. Johnson and Dr. Robert M. Chanock prepared in rhesus kidney cell cultures a pool of respiratory syncytial (RS) virus by methods described in detail in an accompanying paper. On several occasions in the human volunteer work, at the time of use the amount of RS virus in individual samples was measured in Hep-2 cells and was found, depending upon the sample examined, to be 80 to 320 $TCID_{50}$ (tissue culture infectious doses) per ml of material. In the first of two volunteer studies, 2.0 milliliters of the RS infected rhesus kidney cell preparation were sprayed into the nose and throat of each of 12 volunteers to determine the clinical and serologic response of the volunteers to nasopharyngeal instillation of RS virus. Three volunteers, who were housed in separate rooms on the same ward as were the 12 test subjects, served as controls and received no infectious inoculum. The subjects were bled several days before and several weeks after inoculation to obtain sera for use in serologic tests. After the experiment was completed, Sweet and Hilleman (5) reported their findings on the frequent occurrence in rhesus kidney cell cultures of vacuolating virus, the presence of which could be detected by use of a suitable indicator host, i.e., cell cultures of the kidney of the grivet monkey. Examination of the RS pool in the grivet cell system showed that the vacuolating virus was present in appreciable amounts. The relative amounts, measured by the accepted techniques, of two viruses in the inoculum are shown in Table 9. Thus, when 2.0 milliliters of the test material were given by the nasopharyngeal route, each of the volunteers received, in addition to the RS virus, 10,000 tissue culture infectious doses of the vacuolating virus.

TABLE 9. Results of Examination of RS Virus Pool Prepared for Human Use for Presence of Two Viruses

Virus	Indicator Host Cell	$TCID_{50}$/ml of RS Pool
RS	Hep-2	80–320
Vacuolating	Grivet kidney	5,000

TABLE 10. Vacuolating Virus Neutralizing Antibody Titers in Sera on Subjects in RS Volunteer Study

Inoculum	Date Inoculated	Subject	"Vac" Virus-neutralizing Antibody Titer 6/16/60	7/11/60
RS virus 160–640 $TCID_{50}$	18 June 60	1	<5	<5
		2	<5	5
		3	<5	5
		4	<5	10
		5	<5	<20
		6	<5	>20
		7	<5	<5
		8	<5	<5
		9	<5	<5
		10	<5	5
		11	<5	10
Vacuolating virus 7,500 $TCID_{50}$	23 June 60	12	<5	>20
None	—	13	<5	<5
		14	<5	<5
		15	<5	<5

Neutralization tests with pre- and post-inoculation sera employing 100 tissue culture infectious doses of vacuolating virus were carried out in cultures of grivet kidney cells with the results shown in Table 10.

In the first group of six volunteers (subjects 1 to 6 in Table 10) inoculated on June 18 with rhesus kidney cell material containing 640 units of RS virus and 10,000 units of vacuolating virus, only one of the six failed to respond to inoculation of the contaminating virus with development of measurable amounts of specific antibody. Neutralizing antibody was detected in the post-inoculation sera of five of the six volunteers in titers ranging from 1 in 5 to greater than 1 in 20. While sig-

nificance of a neutralizing antibody titer of 1 in 5 might be questioned, a titer of 1 in 20 is an indication of antigenic activity in man of the vacuolating virus when introduced in this experiment by the nasopharyngeal route.

In another group of six volunteers (subjects 7 to 12 in Table 10) inoculated five days after the first group with another sample of the same RS pool, three of six responded to the vacuolating virus component of the inoculum with development of neutralizing antibody, whereas none of the three control volunteers housed with the test subjects during the time of the experiment, and who had received no infectious inoculum, were found to have neutralizing antibody directed against the vacuolating virus in either the first or the second serum specimen. In another study, not shown in Table 10, of 15 volunteers inoculated by the nasopharyngeal route with the RS pool six responded with development of neutralizing antibody directed against the vacuolating virus. Three of these individuals had antibody titers greater than 1 in 20.

From the point of view of one interested in latent viruses, it might be concluded, from the over-all experience in these volunteer studies, that development in human subjects of neutralizing antibody directed against the new vacuolating virus, following nasopharyngeal instillation of rhesus kidney cell material infected with this agent, suggests proliferation of the virus in man under the experimental conditions employed. This finding is in contrast with results of tests performed in our laboratory with sera obtained from children and adults who had received orally live polio vaccine contaminated with vacuolating virus. None of the post-vaccination sera from 15 children and from 28 adults contained neutralizing antibody directed against vacuolating virus. These data, as well as those of Dr. Sabin (6), suggest lack of infectiousness for man of the vacuolating virus when administered by the oral route.

An additional experiment was performed primarily to determine whether or not the respiratory illness in the test volunteers occurring after nasopharyngeal instillation of the test material resulted entirely or partially from interaction, either direct or indirect, of one virus upon the other in the dually infected inoculum. For this determination, two samples of the dually infected rhesus kidney cell preparation were treated individually with antiserum containing antibody directed against one or the other of the viruses. By this technique singly infected samples were obtained for use in volunteer work. Of eight volunteers who received RS virus alone, two experienced clinical respiratory disease. These two and four others, in the weeks following inoculation, developed antibody rises to RS. In all, six of the eight were infected by RS. None of the eight individuals who received vacuolating virus alone experienced respiratory disease in the months following inoculation and none made antibody directed against RS, but all eight responded to the inoculum by development of vacuolating virus antibody in titers ranging from 1 in 5 to greater than 1 in 20. From these data, there seems to be justification in assuming that presence of the vacuolating agent in the RS pool did not play a measurable part in the production of respiratory disease in the individuals who received the RS-vacuolating virus mixture.

DR. VERNON KNIGHT: Dr. Robert M. Chanock, Laboratory of Infectious Diseases, will describe the results of our experiments from a virological standpoint, with reference to the report of Dr. Morris.

DR. ROBERT M. CHANOCK: Respiratory syncytial (RS) virus was first recovered in 1956 by Dr. Morris from a chimpanzee during an outbreak of coryza in these animals (7). In 1957 we recovered the agent from

TABLE 11. Recovery of Respiratory Syncytial Virus, Washington, D. C., March to July, 1960

Diagnosis	0–6 Mo.		7–12 Mo.		13–24 Mo.		25–48 Mo.		49 Mo. +		Total	
	Tested	Pos	Tested	Pos	Tested	Pos	Tested	Pos	Tested	Pos	Tested	Pos
Bronchiolitis or Pneumonia	40	57%	30	20%	22	14%	4	0	10	20%	106	32%
Minor respir. illness	32	19%	24	17%	30	10%	40	12%	33	3%	159	12%
No respir. illness	79	0	32	3%	56	2%	58	2%	47	2%	272	1%

No. of RS isolates from bronchiolitis, pneumonia, and minor respiratory illness = 53.
No. of RS isolates from no respiratory illness (control group) = 4.

infants and children with pneumonia and croup (8, 9).

The virus is medium sized, i.e., 90 to 140 millimicrons, and is sensitive to inactivation by ether (8). Infection of human cells in tissue culture results in the formation of syncytia or pseudo-giant cells (8). It is this property for which the agent is named.

Although the RS virus has been known since 1956–57, conclusive evidence that it causes respiratory illness in man has been obtained only recently. While the current volunteer studies were being planned and executed, it was discovered that infection with RS virus was responsible for a considerable proportion of bronchiolitis and pneumonia among infants and children in the Washington, D. C., area. Dr. Kapikian has just summarized our observations on the outbreak of pneumonia associated with RS infection which occurred in a closed nursery population in April and May, 1960. Shown in Table 11 is a summary of the RS virus experience at Children's Hospital in Washington, D. C., during March to July, 1960. These studies were carried out in collaboration with Drs. R. Parrott, A. Vargosko, and H. Kim (10). The virus was recovered from 32% of patients hospitalized with bronchiolitis or pnuemonia and from 12% of infants and children with predominantly febrile respiratory disease not severe enough to warrant admission to the hospital. In the age group under six months, virus was recovered from 57% of infants with bronchiolitis and pneumonia. RS virus was recovered significantly less frequently from comparable control individuals without respiratory disease. These findings suggest that the agent was etiologically associated with a considerable amount of serious febrile respiratory disease in infants and children during March to July, 1960.

As shown in Figure 3, infection with RS virus was also common in the Washington, D. C., community during the previous years of 1958 and 1959. It is of interest that peaks of bronchiolitis during the past three years have coincided with periods of RS virus activity in the community (11). Since the complement fixation (CF) test is only 50% efficient in the younger age group, the actual contribution of RS infection to hospitalizable pediatric respiratory illness is probably twice that shown in Figure 3. During 1959 we observed serologic evidence of infection in adult college students (12) at a time when infection was at its maximum in infants and children (11). This observation, coupled with the recent evidence that RS virus causes illness in infants and children, prompted us to examine the role of this agent in adult illness. As a first step in this direction studies were carried out with adult volunteers from the Federal Prison system (2, 13).

Table 12 is a summary of the results of

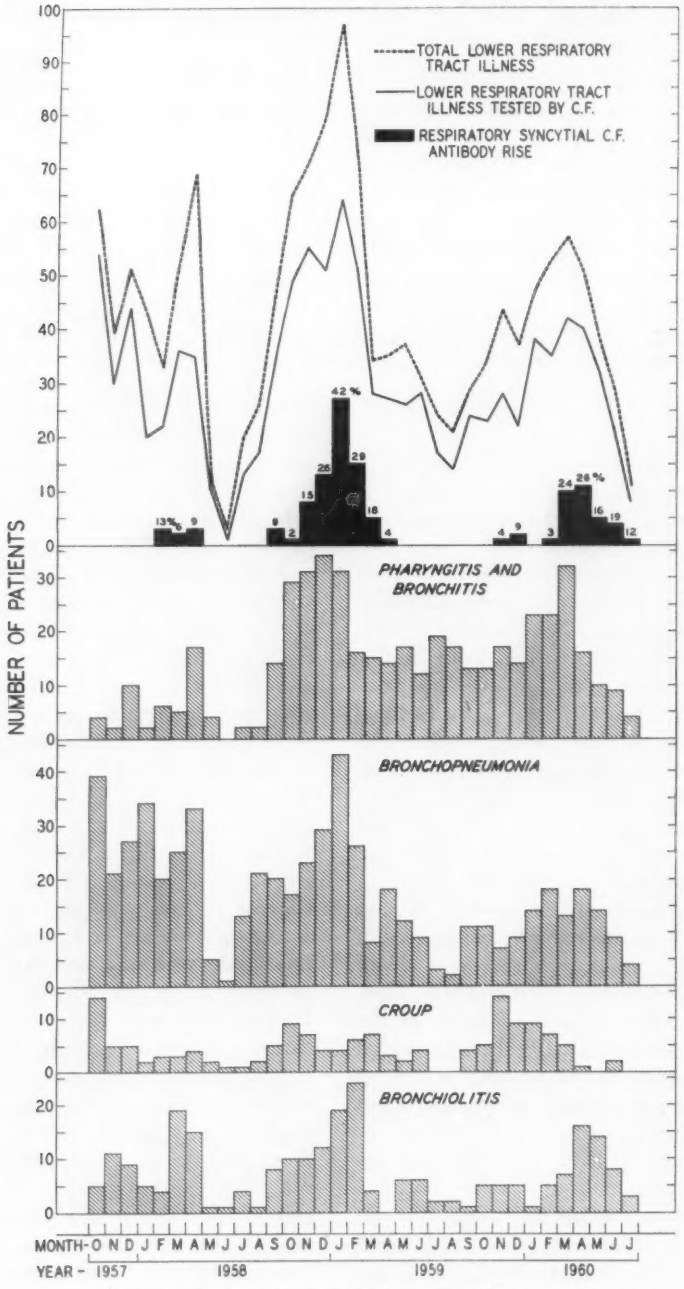


FIGURE 3. RS serology in children, 1957–1960 (9).

TABLE 12. Summary of RS Volunteer Studies

Exp.	Inoculum	No. Tested	Infection: Virus Isolation	Infection: Antibody Rise*	Infection: Total	Upper Respir. Illness
#1	Virus†	12	11	7	11	7
	No virus	12	0	0‡	0	0
#2	Virus†	15	11	8	12	9
#3	Virus†	8	5	3	6	2
	Virus + antiserum	8	0	0	0	0
Total	Virus	35	27 (77%)	18 (51%)	29 (83%)	18 (51%)
	Control (no virus or Virus + antiserum)	20	0	0§	0	0

* Neut. and/or CF.
† 160–640 $TCID_{50}$.
‡ Only three of this group tested serologically.
§ Only 11 of this group tested serologically.

these studies. A total of 35 volunteers received 160 to 640 tissue culture doses of RS virus by the oral and nasal route. The inoculum represented second monkey kidney tissue culture passage virus. Eighty-three per cent of the volunteers were infected as evidenced by virus isolation, development of a rise in antibody, or both. Virus was recovered from 77% of the volunteers. Approximately one-half of the volunteers developed a clinically definable illness as described by Dr. Kravetz. The control volunteers who were inoculated with sterile uninfected tissue culture fluid did not become infected nor did they develop illness.

The presence of vacuolating virus as a contaminant in the inoculum was not recognized until the second experiment had been completed. A third experiment was then designed to determine whether the RS virus or the vacuolating virus was responsible for the cold-like illnesses which had been observed. Eight volunteers received RS virus alone; in this instance the vacuolating virus was neutralized by specific serum. The other eight volunteers received only vacuolating virus, the RS virus being neutralized by specific serum. Two of the eight volunteers given RS virus developed only colds, while none of the eight volunteers who were given vacuolating virus only became ill. This suggests that the RS component of the inoculum was responsible for the illnesses produced in the first two experiments.

As shown in Table 13 illness occurred more often in those volunteers who shed virus for a long interval than in persons from whom virus was not recovered or who shed virus for a short interval. Only two of eight volunteers who did not yield virus and one of eight who shed the agent for one to two days developed illness, whereas 15 of 19 persons who shed virus for three to six days became ill. The correlation between duration of virus shedding and occurrence of afebrile upper respiratory disease also supports the etiologic role of the RS agent in such illness.

TABLE 13. Relation of Illness to Length of Time RS Virus Detectable in Pharynx

No. of Days Virus Recovered	No. of Volunteers	Illness: +	Illness: 0	Duration of Illness (Days)
0	8	2*	6	2,3
1–2	8	1	7	4
3–4	10	8	2	1,3,4,4,5,6,7,7
5–6	9	7	2	4,4,5,6,7,7,7

* One volunteer developed a rise in neutralizing antibody.

TABLE 14. Relation of CF Antibody to Recovery of RS Virus and Occurrence of Illness in Volunteers

CF Antibody Rise	Number of Persons with Indicated Pattern: Virus Recovered +	Virus Recovered 0	Illness +	Illness 0
+	14	0	14	0
0	13	8	4	17
Total	27	8	18	17

The occurrence of illness also correlated with the development of complement fixing (CF) antibody as shown in Table 14. All 14 volunteers who developed a complement fixing response became ill, whereas only four of 21 complement fixing negative individuals developed respiratory symptoms. These findings suggest that complement fixing antibody develops predominantly in those persons whose infection is severe enough to result in clinical illness. Virus recovery also correlated with complement fixing antibody response.

All adults thus far tested possess neutralizing antibody for RS virus. This suggests that the infections which occurred in the volunteers were reinfections, and that the associated illness represented the consequences of such reinfection. As described previously, infection with RS virus early in life frequently results in febrile illness with lower respiratory tract involvement. In this study, infection of adult volunteers was associated with mild afebrile illness, a result which is compatible with the concept of reinfection. Prior to virus challenge, the neutralizing antibody titer of the volunteers varied from 1 : 16 to 1 : 256. Within this range, as seen in Table 15, there appeared to be no correlation of antibody level with virus excretion or occurrence of illness.

TABLE 15. Relation of Prior Neutralizing Antibody Status to Virus Recovery, Antibody Response, and Illness

Reciprocal Neut. Antibody Prior to Virus Challenge	Number of Persons with Indicated Pattern: Virus Recovery +	Virus Recovery 0	Neut. Antib. Rise +	Neut. Antib. Rise 0	Illness +	Illness 0
16–32	17	5	13	9	10	12
64–256	10	3	5	8	8	5

The results of these volunteer studies suggest that RS virus is capable of inducing cold-like illness in adults. The actual importance of this agent in the over-all respiratory disease picture in adults must await the study of such naturally occurring illness. We do not wish to impart the impression that RS virus is *the* common cold virus. As shown in Table 16 at least six distinct viruses, belonging to three different virus groups, have been shown to be capable of producing colds in volunteers. This list represents a mere beginning.

TABLE 16. Viruses Which Have Produced Mild Upper Respiratory Illness in Volunteers

Group	Virus
Myxovirus	Para influenza 1 Para influenza 3
Enterovirus	Coe (coxsackie A 21) FEB HGP
No known relatives	RS

DR. VERNON KNIGHT: As a clinician concerned with this investigation, two or three applications occur to me. We were most impressed that there was no secondary spread outside the infected rooms. The Clinical Center Infection Committee, of which I am a member, has often had great concern about the spread of various kinds of infectious diseases in the hospital: staphylococcus, other bacteria, and viral agents.

RS disease in adults is a benign infection which we can produce at will. Using virological and serological techniques, an in-

fection rate of 83% may be produced. This type of investigation thus offers a device for evaluating our methods for isolation of patients from infectious disease. While the spread of bacteria and the spread of this particular virus may not be parallel, at least here is a way to approach something that has defied thoughtful scientific examination for a long time.

I believe a real approach to the chemotherapy of viral diseases will be made in the future. We have in this particular viral illness a basis for evaluation of the efficacy of an antiviral agent.

The same reasoning would apply to the evaluation of a vaccine. We have been concerned by the fact that infection is as severe in the adult patient with a high antibody titer as in the one with a low titer. This will have to be evaluated further.

Dr. Robert Huebner, Chief of the Laboratory of Infectious Diseases, will comment.

DR. ROBERT HUEBNER: All these studies present a fairly clear picture of a virus that causes respiratory disease with a four-day incubation period which might distinguish it from some other viral infections. However, the RS virus is similar, in the incubation period, to the para-influenza viruses.

We would like to know the extent to which respiratory syncytial virus, the parainfluenzas, the adenoviruses, the enteroviruses, and other agents contribute to the large, ill-defined picture of common undifferentiated respiratory diseases.

There are various factors which influence our observations. The time period of the study is important. Another factor is age, as was demonstrated in these studies. These viruses spread more readily in young members of our society than they do in the old and may cause more or less severe illness. A third factor is place. If one looks in the military recruit population one finds that in this age group (which is very much like that in the university population) adenoviruses types 4 and 7 are very important causes of respiratory disease. If one looks at a university population in cross section over a period of time, as Evans has done in Wisconsin, he finds that these agents are of virtually no importance. Therefore a great deal of what we know about these viruses depends on time, circumstances, and age of the populations studied.

A recent study at Children's Hospital (Washington, D. C.) showed that about 35% of the respiratory illness during a given period may be accounted for by parainfluenza 1 and 3, influenza A, and adenoviruses. When one adds to that Dr. Chanock's and Dr. Kapikian's data on respiratory syncytial virus, this percentage increases perhaps to 45. If one adds to this the primary atypical pneumonia agent which also occurs in children, it might go as high as 50%. If we repeated these studies five years from now we might well have changes in this picture. Another important problem is that of modification of experiences of this sort. I think we have reached a point where we could hope to modify the disease experience of children, if we had a potent and effective vaccine. But such a vaccine would have to include 30 or 40 viruses in order to have a reasonable chance to influence childhood respiratory diseases to any appreciable extent.

DR. VERNON KNIGHT: Dr. Joseph E. Smadel, Chief, Laboratory of Virology and Rickettsiology, Division of Biologics Standards, is here and I wonder if he will comment.

DR. JOSEPH E. SMADEL: I want to take a moment to explain why the vacuolating agent is a matter of considerable importance. As far as the discussion went today it would appear that this agent bothers only tissue culture virologists. Actually this particular agent probably has more to do with the delay in the availability of com-

mercial production of live polio virus vaccine in the United States than any other single technical problem. It is information collected adventitiously during such experiments as you have heard described today, which will have an important bearing on the eventual decision as to whether vacuolating virus is or is not of vital importance if present in live viral vaccines prepared from monkey tissue cultures.

It now seems as if the vacuolating agent is a lesser deterrent in the manufacture of vaccines than was initially supposed. The data presented today by Dr. Morris clearly indicate that under certain conditions, i.e., inoculation by the respiratory route with a fairly large dose (ten thousand infectious units), this agent is capable of infecting man but not of producing obvious disease.

It may be noted that many of the live polio vaccines used around the world in millions of people have had some vacuolating virus in them. Apparently the vacuolating agent is not very pathogenic for man or we would have found out about this earlier. However, the completeness of the epidemiological and clinical observations left much to be desired in many of the geographic areas where live vaccines have been used on a large scale. Hence, some mild affair may have occurred without our knowing it.

On the other hand, Dr. A. B. Sabin and Dr. Robert M. Friedman, in the Division of Biologics Standards, indicate that the vacuolating agent is not infectious for man when given in small amounts by the oral route. Among small groups of carefully studied persons who had been fed live polio vaccine containing vacuolating virus, none developed antibodies against the vacuolating agent. Moreover, examination of stool specimens from such persons revealed no evidence of multiplication of the vacuolation virus in their intestines.

These things add up to the conclusion, I believe, that this particular indigenous monkey agent can multiply in man in certain circumstances. Therefore it is mildly infectious to man. But in other circumstances it is incapable of multiplying and therefore is not infectious. In no circumstances does it appear to be particularly pathogenic.

As a result of studies of another type, Dr. Casper W. Hiatt of the Division of Biologics Standards has demonstrated that vacuolating virus is readily inactivated by photodynamic processes which do not appreciably affect the activity of the poliovirus itself.

In June 1960 when vacuolating virus was first described, everyone in the polio field was pessimistic about the possibility of eliminating it from live vaccines. I think the virus still presents a problem today, but it appears to be one that can be solved.

DR. VERNON KNIGHT: Dr. Hugh E. Evans of the Laboratory of Clinical Investigations will summarize this conference.

DR. HUGH EVANS: The respiratory syncytial virus was initially isolated from chimpanzees with coryza and infants with croup and pneumonia in 1956 and 1957 by Dr. Morris and Dr. Chanock. The virus is of medium size (90 to 140 millimicrons) and is inactivated by ether. It produces characteristic syncytia in Hep-2 tissue culture.

The illness produced in adults and infants has a four-day incubation period. The clinical syndrome depicted by Drs. Chanock, Parrott, and Kapikian in children includes pneumonia, bronchiolitis, fever, cough, and coryza. The fever lasted for an average of four days and often reached 103 F. In contrast, among 35 adult volunteers studied by Dr. Kravetz, all of whom had a demonstrable antibody titer to this virus, only 18 became ill and they had nothing more severe than a mild common cold.

These studies suggest that RS virus is an important cause of relatively severe respira-

tory disease in children, especially in those cases which follow a first exposure. In adults the artificially induced disease is mild and the evidence is that it represents reinfection illness. It seems possible that previous infection reduced the severity of subsequent attacks in the adults and this may be the pattern of natural occurrence of RS virus infection and many other of the common respiratory viral illnesses of man.

Dr. Morris demonstrated infection of volunteers with the simian vacuolating virus (SV_{40}) which was contained in some of the rhesus monkey kidney inocula of RS virus. The clinical studies suggested, however, that this virus did not cause illness. Dr. Smadel pointed out that the presence of simian vacuolating virus in live polio vaccine has caused concern, but its apparent lack of production of illness in the volunteers is an encouraging finding.

Summario in Interlingua

Le virus syncytial respiratori esseva isolate initialmente per Dr. Morris e Dr. Chanock in 1956 e 1957 ab chimpanzes con coryza e infantes con croup e pneumonia. Le virus es de largor mediocre (90 a 140 millimicron) e es inactivate per ethere. Illo produce characteristic syncytios in histoculturas de epithelio human.

Le morbo producite in adultos e infantes ha un periodo de incubation de quatro dies. Le syndrome clinic delineate pro casos infantil per Drs. Chanock, Parrott, e Kapikian include pneumonia, bronchiolitis, febre, tusse, e coryza. Le febre durava me'iemente quatro dies e frequentemente illo attingeva 103 F. Per contrasto con isto, in 35 voluntarios adulte studiate per Dr. Kravetz (le quales omnes habeva demonstrabile titros de anticorpore anti le virus), solmente 18 cadeva malade, e mesmo istes habeva nihil plus sever que un leve episodio de catarrho commun.

Iste studios indica que le virus syncytial respiratori es un causa importante de relativemente sever morbos respiratori in juveniles, specialmente in casos post exposition initial. In adultos le morbo, in forma artificialmente inducite, es leve, e le evidentia supporta le conception que illo representa un morbo de re-infection. Il pare possibile que le previe infection reduceva le severitate del subsequente attaccos, e isto es forsan le schema normal del occurrentia natural de infectiones per virus syncytial respiratori e de multe alteres del commun morbos virusal respiratori in le homine.

Dr. Morris demonstrava infection de voluntarios con le vacuolante virus simian (SV_{40}) que esseva continite in certes del inoculos de virus syncytial respiratori in ren de rheso. Tamen, le studios clinic pareva indicar que iste virus non es un causa de morbo. Dr. Smadel signalava que le presentia de virus SV_{40} in vive vaccino anti poliomyelitis ha essite le causa de inquietude, sed su apparente incapacitate de producer pathologia in le voluntarios es un constatation incoragiante.

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On Vitality of Thought in the Medical Profession

THIS relationship between the infinite and the finite is what I was coming to. Our minds are finite, and yet even in these circumstances of finitude we are surrounded by possibilities that are infinite, and the purpose of human life is to grasp as much as we can out of that infinitude. I wish I could convey this sense I have of the infinity of the possibilities that confront humanity—the limitless variations of choice, the possibility of novel and untried combinations, the happy turns of experiment, the endless horizons opening out. As long as we experiment, as long as we keep this possibility of progressiveness, we and our societies are alive; when we lose them, both we and our societies are dead, no matter how externally active we and they may be, no matter how materially prosperous they and we may appear. And nothing is easier to lose than this element of novelty. It is the living principle in thought, which keeps all alive."

. . . . . .

This led to a discussion of the vitality of thought in the medical profession in our own time, how rapidly their science is moving, and yet they will tell you they know very little. He said:

"One of the most advanced types of human being on earth today is the *good* American doctor."

"Because in him science is devoted to the relief of suffering?"

"I would place it on more general grounds: he is sceptical toward the data of his own profession, welcomes discoveries which upset his previous hypotheses, and is still animated by humane sympathy and understanding."

"But for their advance," said I, "I would have been dead twenty years ago, of appendicitis. In 1892 the victims died. Now it is rated a 'minor' operation."

"But for a discovery in medicine only three years old," said Whitehead, "I would have been dead six weeks ago." He had had pneumonia and been saved by the new drug.—*Dialogues of Alfred North Whitehead as recorded by Lucien Price,* Little, Brown and Company, in association with The Atlantic Monthly Press, Boston, 1954, pp. 163–165.

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EDITORIALS

The Image of the American Physician

THERE CAN BE LITTLE DOUBT that in recent times the image of the American physician in the public mind, and especially as portrayed in the public press, has undergone a deplorable change. He has been depicted at worst as a reactionary money seeker and at best as a well-motivated but narrow-minded participant in a changing social scene—a professional unable to see beyond the immediate problems of diagnosis and treatment and fee for same.

". . . the doctor may be a learned man in his own field. But in general knowledge he is the worst-educated of our professional men. . . . Eternally busy with individuals and their private troubles, he seldom participates in civic problems" (1).

It was against this discouraging background of public opinion that the Editor, during a course of summer vacation reading, came across a happier characterization from the pen of no less an observer than the late philosopher, Alfred North Whitehead (2). The full quotation is given on page 525, but the key sentence concerning the vitality of thought in the good American doctor is as follows:

". . . he is sceptical toward the data of his own profession, welcomes discoveries which upset his previous hypotheses, and is still animated by humane sympathy and understanding."

This is the sort of eulogy that warms the cockles of every medical heart. But is it deserved? Are we *good* doctors? Are we sufficiently sceptical? Do we welcome findings which upset previously held opinions? Are we animated by humane sympathy and understanding? In a word, does the American physician of today retain the vitality of thought necessary to adapt himself and his activities to the "new winds" of social and scientific changes that are blowing through this decade of the Sixties? We hope so.

Many factors enter into this changing social and scientific scene. The population is increasing (and much faster relatively than is the number of physicians). There are proportionally many more older citizens. The cost of medical care, especially hospital care, has skyrocketed. And most of all, the accelerating expansion and complexity of medical and biological science have altered to an almost unbelievable extent the potential quality of medical care, an optimal medical care that the public has been educated to expect and to demand. These social factors call irresistibly for experiments in improving the social mechanisms for providing medical care, experiments in group practice, in group insurance, and in the thorny problem of use of public funds to pay for medical treatment. Because these are social experiments in which the physician must play a central role, it would be well for him to have a major voice in their design. It is encouraging that President Larson of the American Medical Association stated this year in his inaugural address (3) in which he emphasized the professional spirit:

"This spirit is nourished by the air of freedom—freedom to think, to act and to achieve, according to one's abilities. It therefore contains elements of both conformity and nonconformity. It emphasizes conformity to the principles of scientific truth and ethical conduct. It also recognizes the rights and potentialities of the rebel or maverick who may have a new idea, a different method, a fresh viewpoint."

This statement was given wide publicity by the weekly newsmagazine *Time* (4). Let us

hope that it is justified and that the mental vigor of our profession will rise to meet the challenge of this windy decade.

As the problem of the distribution of medical care has intensified, the image of the American physician has changed for the worse; but the physician himself has surely changed for the better. This change was excellently described by Dr. Dana Atchley some years ago in *The Atlantic Monthly* (5). He pointed out that over the last forty years the physician has changed from being an empiric follower of a tradition in which diagnosis was a mere cataloging of descriptive labels to being a scientist eager to understand the basic mechanisms of disease and truly concerned with the whole patient, a concern that leads to the compassion so necessary for good medical care. As the physician has exchanged the role of magician for that of scientist a new integrity has entered into and has enriched his relationship with his patient. Every discussion of the good doctor ends up emphasizing his compassion and understanding, in short, his personal relationship with his patient. In his convocation address to The American College of Physicians this spring (6) President Keefer put his finger on this relationship as the key to the problem of the changing image of the physician:

"The only image of the physician that really counts in society is the one created by the patient as a result of his personal relations with his doctor."

Alfred North Whitehead, by his own admission, had just survived a bout of pneumonia. From the image projected by the philosopher he must have been cared for by an able and compassionate physician, a *good* American doctor. The question is, can *all* patients obtain such care? Are there *enough* good doctors? Can the economic burden of modern medical care be made bearable? When the answers to these questions are in the affirmative, the public image of the American physician will take care of itself.

J. R. E.

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The Control of the Secretion of Pancreatic Juice and Bile

The importance of pancreatic juice and bile in the normal digestion of food is generally accepted. Physicians are familiar with the steatorrhea and malnutrition of patients with chronic pancreatitis and obstruction of the common bile duct as examples of derangements of the normal conditions. In recent years the study of secretion as an example of active transport has been applied to the mechanisms of formation of bile (1), and carbonic anhydrase inhibitors have been used to study the formation of pancreatic juice and bile (2, 3). Such studies have led to the concept that bile is a mixture of bile salts actively transported by the hepatic cells and an electrolyte solution resembling a filtrate of plasma which reaches the biliary radicles by passive diffusion. For pancreatic juice, the acinar cells appear to contribute the enzyme precursors, but the water and electrolyte are derived from cells lining the

ducts. An appropriate amount of these secretions enters the intestinal lumen for the digestion of food, yet the flow is much reduced or absent during conditions of rest; the control of these secretions in the intact mammal has been studied relatively infrequently in Western Europe and in the United States.

Pavlov and his school developed experimental surgical techniques for the study of pancreatic secretion and bile in unanesthetized animals (4). He demonstrated that stimulation of the peripheral end of the cut vagus nerve in the unanesthetized dog resulted in a flow of pancreatic juice from a pancreatic fistula. He concluded that both vasoconstrictor and secretory fibers to the pancreas were present in the sympathetics. A curious similarity in the hourly rate of pancreatic secretion and the entry of bile into the intestine of the dog in response to feeding was noted.

These results emphasized the role of the nervous system in the control of glandular secretion, but the observations of Bayliss and Starling (5) in 1902 opened an entirely new approach. They demonstrated that an extract of intestinal mucosa injected intravenously produced a profuse flow of pancreatic juice in the dog. They noted also that this preparation doubled the rate of bile secretion. The similarity of this effect to that obtained by injecting hydrochloric acid into the duodenum led them to the conclusion that the effect of acid was mediated by secretin, as they named the material. These experiments began the series of investigations, still in progress, to determine the chemical structure of secretin and its role under normal circumstances.

Thomas (6) pointed out that secretin only accounts for the pancreatic response to acid in the duodenum. The pancreatic juice under such circumstances is relatively weak in enzymatic activity in contrast to the pancreatic juice after a normal meal. In 1943, Harper and Raper (7) reported that a second extract from intestinal mucosa would produce a marked increase in the enzymatic activity of pancreatic juice and named it pancreozymin. Harper (8) has subsequently remarked that this preparation also contained a pepsin stimulant, cholecystokinin, and probably substance P. Further study has been impeded by difficulties in obtaining pure substances. Professor Jorpes, who has contributed so much to advances in purification of these substances, has discussed this aspect of the problem earlier in this issue of the ANNALS. The most purified secretin still exerts a choleretic effect, a "side-effect" analogous to the antidiuretic activity still found with synthetic vasopressin. Harper and his clinical associates proceeded to get considerable experience in the use of pancreozymin and cholecystokinin in clinical diagnosis (9, 10).

The study of the control of bile secretion also led away from the nervous system. Whipple (11) found that the only real cholagogue was the bile acid fraction of bile. He also noted that a meat diet increased bile flow. The question of whether secretin is a true choleretic or merely a hydrocholeretic increasing the watery portion of bile has probably been settled in favor of the former view (12).

The question of the importance of these humoral factors in the intact subject under normal conditions remained. The choleretic activity of bile salts has been demonstrated repeatedly in bile fistula preparations. Wang and Grossman's elegant experiments with the transplanted pancreas in the dog indicated that a blood-borne factor which was released following feeding was a powerful stimulant to both the volume and enzyme activity of pancreatic juice (13).

Yet to be studied was the question of whether the nervous system made a contribution of importance to the control of secretion from the pancreas and liver. Thomas (6) noted that cutting the vagus or splanchnic nerve supply to the pancreas produced little impairment in pancreatic secretion but that large doses of atropine would reduce the response to many stimuli.

He suggested that local reflexes might be of some importance. Comfort and Osterberg (14) used acetyl-beta-methylcholine (mecholyl) to stimulate pancreatic secretion as a clinical test in man, and Kyle, Machella, Lorber, Hilsman, Reinhold, and Brown (15) used urecholine with a resulting increase in both volume and enzyme activity. Dreiling and Janowitz (16) employed newer anticholinergic drugs to markedly reduce the response of the human pancreas to secretin. Bykov (17), in a current Russian textbook of physiology, reported that ergotoxin almost completely depressed the pancreatic response to intraduodenal acid.

These observations certainly suggest that a local nervous mechanism may be involved in the action of secretory hormones on the pancreas. It is tempting to draw a parallel with the relationship of gastrin and the vagus in gastric secretion, where a synergistic action of nervous and hormonal factors appears likely.

Additional evidence to implicate the nervous system in control of pancreatic secretion has been obtained. Harper, Kidd, and Scratcherd (18) have observed increased enzyme activity in pancreatic juice following stimulation of either afferent or efferent fibers in the vagus. In a review of the subject, Harper (8) indicates that there may be species differences in the importance of the cephalic phase of pancreatic secretion. In any consideration of nervous control, a secondary mechanism acting through control of blood supply must be considered. Tankel and Hollander (19) doubt that pancreatic secretion is dependent upon blood flow under normal conditions.

Hokin and Hokin (20) have suggested a mechanism for pancreatic secretion in which acetylcholine has been assigned the role of acting on the membranous fragments of the microsomes to render the enzyme and substrate more accessible in phospholipid metabolism.

Evidence for the role of the nervous system in the secretion of bile is very scanty. Tanturi and Ivy (21) found that splanchnic stimulation decreased bile formation coincident with vasoconstriction in anesthetized dogs. Lack of correlation between increases in blood flow and increased secretion of bile makes it difficult to determine the possible secondary effects on the secretion of bile exerted by the nervous system on the circulation. Snyder (22), using a bioassay, noted that vagal stimulation in the turtle released acetylcholine from the liver. Cannon and Uridil (23) demonstrated that stimulation of the splanchnic nerves in the cat released an epinephrine-like substance from the liver. Russian workers (24, 25) have reported that decortication and the stimulation of mechanoreceptors in the intestine modify the secretion of bile in chronic experiments in dogs.

Whereas pancreatic secretion has been correlated very well with feeding, attempts to demonstrate the choleretic effects of feeding in man were unsuccessful (26). The possibility of humoral agents in the intestinal mucosa other than secretin has been suggested by Friedman and Snape (27).

In summary, humoral factors have been shown to be of major importance in the control of pancreatic and biliary secretion in experimental animals and in man. Anticholinergic drugs have been found to effectively reduce humorally stimulated pancreatic and biliary secretion. The possibility of local reflex mechanisms playing a role in secretion remains. Nervous control per se has not been shown to play an important part in the control of pancreatic and bile secretion under normal conditions in man but the critical experiments to demonstrate such control have not yet been performed.

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Corticosteroids and Varicella Pneumonia; or Skepticism, the Chastity of the Intellect

THE DISCUSSION, in this issue, of pneumonia complicating varicella presents one of the largest series of these cases yet reported. Many clinicians have suspected that pneumonia is a common complication of varicella but since the findings in clinical examinations of the lungs have been few and minor, more accurate definition of the lung lesions by X-ray examination has rarely been sought. Substantiation of

the pneumonia by careful roentgenologic study in a large series of patients has long been needed.

However, the most significant contribution of this report lies in the observation that although none of the patients received corticosteroids, all survived without complications. Pediatricians have noted that, when a few children who were receiving corticosteroids for a coincidental disease developed varicella, the course was often complicated by pneumonia and led to a fatal outcome. Despite such reports, these agents have been advocated for treatment of varicella pneumonia. In the face of such literary and scientific conflict, it is significant that the patients reported by Mermelstein and Freireich (1) did so well without corticosteroids. Again, it is evident that carefully controlled studies are needed before the role of corticosteroids in such therapy can be ascertained. To date, these studies have not been done.

In almost any infectious disease, corticosteroids have a most salutory appearing effect, initially, on the patient. If the patient coincidentally recovers from his infection, the subjective improvement in symptoms is associated in the mind of the treating physician with a specific therapeutic effect. Indeed, this association may well be correct on occasion, but, more often than not, when infectious diseases and corticosteroid therapy have been carefully studied, the indications for corticosteroids have not been substantiated. Further complicating the evaluation of this approach to infectious diseases, one has to recognize that each infectious disease presents an entirely different problem metabolically and therapeutically. Therefore, information obtained from treating one infectious disease cannot always be applied to the treatment of another. Finally, within a particular type of infection, its expression from patient to patient varies markedly. These and similar variations tend to make evaluation of any treatment, particularly corticosteroid, most difficult. The most practical solution to such a dilemma would seem to be a carefully controlled study of alternate cases, such as best can be done in communicable disease centers or by physicians seeing large numbers of patients with a specific infection. Until better elucidation of the value, mechanisms of actions, and complications of corticosteroid therapy can be obtained in varicella pneumonia, the practicing clinician should view with interest but with a certain degree of skepticism the claims that corticosteroids are the agent of choice for pneumonia complicating varicella. In this instance, as so often in medicine, one should recall Santayana's sage comment, "Skepticism is the chastity of the intellect, not to be taken lightly nor surrendered to the first comer."

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Water, Salt, and the Failing Heart

Despite the dramatic advances in cardiac surgery and the development of ever more potent diuretic drugs, the patient with heart disease and edema continues to pose a very real physiologic and therapeutic problem. The pathogenesis of congestive heart failure is still obscure although edema has been recognized for a long time to be an abnormal accumulation in various parts of the body of water, so-

dium, and other extracellular electrolytes. The causal chain of events that leads to this accumulation has been the goal of a host of investigators whose paths have led through many a jungle of hemodynamic, endocrinologic, and biochemical complexities. Let us consider some of the more recent blazings of this pathogenetic trail.

The current era of trail-blazing might be said to have started almost two decades ago when the hemodynamic concept of "backward failure" was first challenged by Starr, Jeffers, and Meade (1) and by Warren and Stead (2). From the observation that the retention of sodium may precede elevation of the venous pressure these workers proposed a sequence of "forward failure"; diminished cardiac output, poor renal blood flow, lowered filtration rate, retention of salt and water. This hypothesis turned attention to the role of the kidney in the genesis of edema. It was soon established by many clinical and experimental studies that the rates of renal blood flow and glomerular filtration were depressed, that the tubular reabsorption of sodium was abnormally high, and that the excretion of the ion was abnormally low. Quite clearly, the patient in congestive heart failure does not excrete sodium and water in a normal manner.

Why and how this should be so, has remained the greater question and the subject of much recent investigation. Some of the answers are being sought in the increasingly complex field of the extrarenal mechanisms for body fluid regulation. As early as 1935 Peters (3) had suggested that the rate of excretion of extracellular electrolytes and water must be sensitive to some function or dimension of fluid volume within the body; in 1948 he went on to postulate that in the edematous cardiac a diminution in "effective blood volume" must stimulate the secretion by the adrenal cortex of a salt-retaining hormone (4). This salt-retaining hormone has since been identified as aldosterone and has been found in excessive amounts in various types of clinical and experimental congestive failure. But the primacy of its role in the pathogenesis of edema in the cardiac patient, and the causal sequence of events leading to abnormal elaboration of the hormone, still are not clear.

Hyperaldosteronism has been demonstrated more consistently in the dog with experimental edema than in the human patient (5). Deane and Barger (6) using dogs with induced tricuspid insufficiency plus pulmonic stenosis, Davis, Goodkind, Pechet, Ball, Yankopoulos, Kliman, and Peterson (7, 8) employing animals with ascites secondary to constriction of the thoracic inferior vena cava, have consistently found a secondary excessive secretion of aldosterone to be associated with the abnormal retention of sodium. Similar findings have been reported in some, but not all, patients with congestive heart failure (9–13); in at least two studies of such patients the aldosterone secretion has been found to be normal (14, 15). In a group of 40 patients with various types of heart failure Wolff, Koczorek, and Buchborn (13) found increased aldosterone activity in two-thirds of the untreated edematous patients. Most of these were patients with "right-sided heart failure"; in "left-sided failure" aldosterone activity was normal. It is perhaps relevant that in the latter type the volume of the accumulated fluid is much more restricted for anatomical reasons.

If excessive secretion of aldosterone is at least one effector mechanism in the production of edema, how has the system of volume regulation gone wrong on the afferent side? What stimulus or what receptor has signaled the need to retain more sodium and water when already there is too much? Despite a great deal of experimental work the regulation of volume is much less well understood than is the osmoreceptor-antidiuretic hormone system for regulation of concentration (16). Recent work has indicated that decreased volume and pressure

in the vicinity of the thyroid-carotid arterial junction leads to increased secretion of aldosterone and hence to retention of sodium and water (17); increased volume and pressure in the right atrium reverses the sequence (18, 19). In such a system the hyperaldosteronism of heart failure would suggest that the pressure deficit in the arterial side overbalances the pressure excess in the central venous side of the vascular system. Unfortunately, there is other experimental evidence that casts some doubt on this neat hypothesis: bilateral cervical vagotomy and denervation of the carotid arterial system (20), and indeed of the entire central arterial tree (21), do not appear to influence the excessive rate of excretion of aldosterone in the dog with experimental edema. The trail of the volume receptors is hot but the quarry is still elusive.

Meanwhile attention has turned again from extrarenal to intrarenal factors that contribute to the low rate of excretion of sodium in congestive failure. In the first place, the kidney itself has been shown to be a source of an aldosterone-stimulating hormone (22), and hence may well contain volume and pressure receptors. It has been suggested, also, that a high filtration fraction with an increase in the oncotic pressure of plasma proteins in the peritubular capillaries might enhance the reabsorption of water and salt from the tubular lumen (23, 24); however, the filtration fraction has not been found to be consistently elevated in experimental or in clinical congestive heart failure (25). An increased sympathetic activity with resultant low renal blood flow has been implicated by Barger and colleagues on the basis of the response to the injection of an epinephrine-norepinephrine inhibitor into the renal artery (26), and on the basis of the effects of graded valvular damage (27) in the dog with experimental heart failure. Excessive proximal tubular reabsorption of sodium, filtered in diminished amounts, may well lead to inadequate amounts of the ion reaching the distal portions of the tubule and hence to lower rates of excretion of sodium and of generation of "free" water (28). Certainly the failure to maintain a sodium diuresis with the aldosterone antagonist, spirolactone, suggests that more than aldosterone is influencing the excretion of sodium in the edematous patient (29).

It is against this background of uncertainty in the pathogenesis of congestive heart failure that two papers in this issue of the ANNALS should be read. Iseri, Balatony, Evans, and Crane present evidence for two kinds of fluid shift from the vascular system of patients in congestive failure. The first is a transfer of whole plasma into interstitial spaces when the patient changes from the recumbent to the upright position; the second is a shift of water alone from plasma during exercise, presumably into muscle cells and presumably due to changes in osmotic activity of cellular solutes. Both experimental variables, upright posture and exercise, are known to exacerbate the edema of heart failure; they may well contribute to the erroneous signals from volume receptors that lead to the retention of sodium and water.

The second paper, by Takasu, Lasker, and Shalhoub, goes far to illuminate the difficult problem of hyponatremia in the cardiac patient. Ever since the advent of the flame photometer facilitated its measurement, a serum sodium concentration at depressed levels has been found in certain edematous cardiacs. In some of these patients it has been known to be a sign of grave prognosis. A decade ago it was recognized by many of us to involve a primary retention of water and probably an abnormal release of antidiuretic hormone due to a changed "set" of the osmoreceptors. Since then much has been learned of "inappropriate" release of antidiuretic hormone in many diseases, of glomerulo-tubular imbalance, and of the generation and excretion of "free" water by the kidney. Takasu and

his colleagues have applied these newer concepts to the problem of the hyponatremic cardiac. By analysis of serial urine osmolalities during the administration or restriction of water they have identified three mechanisms that may operate separately or in combination: lowered setting of the osmoreceptors, sustained secretion of antidiuretic hormone, and glomerulo-tubular imbalance. This differential diagnosis is of more than academic interest; the treatment of these patients is usually a difficult problem. The first two of the above mechanisms call for restriction of water intake, the latter calls for every therapeutic measure that the physician has at his disposal to improve general and renal hemodynamics and renal function. These measures include digitalis, aminophyllin, osmotic diuretics, and rarely—in the patient with evidence of acute peripheral vascular collapse—infusion of hypertonic saline. Improved differential diagnosis renders less desperate the treatment of this often desperate clinical situation.

To physician and physiologist alike the edematous patient with the failing heart is an age-old, ever-present, and still-enigmatic problem. From the first reported case of "backward failure"—Lot's wife (30), to the modern-day edematous patient with "forward failure," the pathogenesis of edema has been the subject of intensive study. We have learned much but there is still much to learn.

J. R. E.

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BOOKS

Book Reviews

Heart Sounds and Murmurs. A Clinical and Phonocardiographic Study. By P. A. Ongley, M.D., M. B. Rappaport, M.D., Howard B. Sprague, M.D., and A. S. Nadas, M.D. 360 pages; 26 × 18 cm. Grune & Stratton, New York, 1960. Price, $9.75.

After an introductory chapter devoted mainly to the technique of making phonocardiograms, this book is divided into four sections. The first presents the history and physics of sound as related to auscultation and phonocardiography and contains much interesting information. The second and third deal with auscultation and phonocardiography and their applications to diagnosis of acquired and congenital heart diseases, respectively. The fourth section is stated to contain miscellaneous information concerned principally with arrhythmias.

The authors have based their book upon study of abundant clinical material. For example, it is stated that more than 150 patients with congenital aortic stenosis have been studied, over 50 with proven tricuspid atresia and 16 with Ebstein's anomaly, in ten of whom phonocardiograms were obtained. Most of the 211 figures include phonocardiograms recorded in conjunction with electrocardiograms and sometimes also apex cardiograms or jugular pulse tracings. These are beautifully reproduced, thus affording an excellent opportunity to study the material presented.

The authors have made many interesting and useful observations on various matters which they express clearly. They point out what they regard as the superiorities of the phonocardiographic apparatus employed by them over other commercial models. They discuss, in a most interesting manner, the values and limitations of various kinds of stethoscopic equipment including such matters as length and bore of tubing.

There is little representation of the fascinating studies of the past few years concerning the genesis of heart sounds and murmurs which have resulted from the addition of intracardiac pressure curves and sometimes intracardiac phonocardiography or other new procedures to the methods employed in the past. The physical and engineering problems concerned in reflecting in phonocardiograms the sound vibrations which develop at the body surface are fully discussed. Transmission to the body surface is also discussed save for the probably important differences in the heart itself as a transmitting agent in systole versus diastole. But the extent of the difficulties encountered by some workers in trying to apply what has been learned concerning the physics of sound to the genesis of heart sounds and murmurs in complex cardiovascular situations would scarcely be suspected by the uninitiated reader. For example, the traditional although often disputed view that the audible portions of first heart sound vibrations are produced in A-V valves as they are moved to the position of closure is stated as though this were an established fact without reference to any alternative explanation for the genesis of the vibrations or the hypothesis that various structures set into vibration may contribute to the sound. Murmurs are stated to be the result of "turbulence" with no mention of other thoughts regarding their genesis which have enlivened some of the symposia of recent years. The authors have altered considerably the concept of what had been called "summation gallop," without indicating the reasons for this change, and without any recognition of the previous use of this term or recent work with newer, more precise methods supporting the validity of the original concept.

Phonocardiography, up to now, has undoubtedly been useful for displaying the time relations of sounds and murmurs to other cardiac events. But the apparatus employed by the authors as well as the other commercial models now available can scarcely rival the human ear in detecting characteristics of sounds with various of their nuances. The signal : noise ratio is such that certain faint murmurs heard in a quiet room by a trained observer are not recorded clearly. Moreover, the short murmur sometimes resulting from incomplete summation of gallop sounds or even at times by the two sound components of atrial gallop, when they fall in the presystolic time range, are easily distinguished by the ear from the presystolic part of the murmur of mitral stenosis, but the machine does not seem to be able to make this differentiation. This appears to be the reason

for the frequent presystolic murmurs, recorded in congenital heart diseases, which rarely pose a problem for the clinician experienced in the interpretation of sounds. When the machine records a short diastolic murmur after a sharp second sound which one cannot hear irrespective of the "masking" effect of the sound, it might be prudent to check the adequacy of damping of vibrations.

Differences of opinion in the field of heart sounds and murmurs, which still has so many unsolved problems, are to be expected. Probably no one could write such a book as this without arousing disagreement. At the present time, students and others who wish to increase their knowledge of the subject will scarcely find so much in one treatise elsewhere.

CHARLES C. WOLFERTH, M.D.

Valvular Disease of the Heart in Old Age. By P. D. BEDFORD, M.D., M.R.C.P. and F. I. CAIRD, D.M., M.R.C.P. 194 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1960. Price, $7.50.

The scope of this excellent little book is defined by its authors as "analysis of a series of elderly patients who were studied by simple clinical means and were found to have valvular disease of the heart." The book deals with 419 persons aged 65 or over admitted to the geriatric unit of the Teaching Hospital Group at Oxford between 1949 and 1956. Only 20% had been thought to have heart disease. About 50% ultimately came to necropsy. The documentation is thorough yet unobtrusive. The authors clearly designate the basis of every observation, supposition or conclusion they make, yet avoid getting the evidence in the reader's way and do not clutter their chapters with undigested material. The pertinent literature is dealt with perceptively, judiciously, and somewhat tartly. Throughout the book, this reader was impressed with its tact, compassion, and sense of proportion.

A number of noteworthy points are made. Auscultatory criteria were at least as effective for the diagnosis of valvular heart disease in the elderly as in younger age groups, but no valve lesion or combination of lesions (rheumatic, luetic, or degenerative) altered the prognosis of elderly patients, unless failure developed. The clinical features of congestive and left ventricular failure in the aged are interestingly dealt with. Atrial fibrillation was a very common cause or accompaniment of failure and often precipitated, like it, by respiratory infection. The commonest symptoms of failure were confusion, cough, and gastrointestinal disturbance.

The authors have strong convictions in behalf of vigorous treatment of congestive failure and infection; anticoagulant therapy for failure, embolism, and atrial fibrillation (which latter they regularly aim to convert); of chronic pyelonephritis as the main cause of severe kidney disease, except for the reversible changes readily produced by congestive failure; of the commonness of pulmonary infarction, with persistent tachycardia as a clue to its presence; and of the rarity of right ventricular failure from emphysema (a bad prognostic situation when it does occur). Their views and experience are presented in a stimulating, graceful, and convincing way. Even when they overstep their bounds, as in discussing the evaluation of mitral stenosis and insufficiency for surgery (page 31), their sources are carefully described and the reader is not misled by statements clearly based on incomplete coverage of a controversial, rapidly moving field.

Cardiovascular physicians and those concerned with caring for old people will find this book good reading, and to these physicians the authors have addressed it. But their little book is also an example of what they assert to be the need for medicine "drowning in an ever increasing torrent of publications:" namely, "greater awareness of would-be authors of the extent of their responsibilities." It is to be recommended also for the general education of senior medical students and residents. Exposure to its compact, restrained, meticulous scholarship and its clinical acuteness should make better doctors, sharper observers, and more critical recorders and readers.

JOHN J. SAŸEN, M.D.

Essential Hypertension: An International Symposium. Held in Berne, June 7–10, 1960, sponsored by the Ciba Foundation. F. C. REUBI, Chairman, K. D. BOCK, M.D. and P. T. COTTIER, M.D., Editors. 392 pages; 21.3 × 14.3 cm. Springer-Verlag, Berlin, 1960. Price, DM 33.80.

The same faces and billings, but a new theater—this is the usual medical symposium, and it differs from events of mime and music and dance only in serving to instruct rather than to entertain. The talks transcribed in this book were properly grave. Only once, to my eye, was this mood broken; this was when Dr. Irving Page noted that

". . . the principle of the 'fur-lined bathtub' is a useful one and I commend it to you. If you keep blondes out of them and your hypotensive patients in them, you will avoid legal complications."

The papers in this symposium were extremely varied in scope; some gave only the direct observations of their authors, others summarized all recent advances in the areas of their concern. Pickering and Platt continue their debate, from evidence in their population studies, on the question of inheritance of "essential" hypertension. Page's review of his "mosaic theory" of hypertension implies what even the non-cognoscenti can guess: that "essential" hypertension is many disorders not now recognized save by their common and final result—the chronic elevation of blood pressure and its sequels. The missionary work of Dahl in home and foreign fields, urges us to drive that old devil Salt from our diets, and with him, his evil son Hypertension; his plea is very convincing. If I listen to Dr. Dahl much longer, my dietary Salt will join those outcasts, Testosterone and Tobacco.

Some of these essayists will not hold the attention of practicing physicians, but many will. Warter comments on the blurred boundary between typical primary aldosteronism and those with hypertension but milder degrees of hyperaldosteronism not due to aldosterone-adenomas. The pharmacology of the newer hypotensive drugs is summarized concisely by Plummer, and Hoobler describes in very specific detail his program for the treatment of hypertension with drugs.

The physician who wishes to review some of the developments in the nosology, physiology, and therapeutics of hypertension from the last five to ten years should find this compact book to be useful; he should not look to it for a systematic account of all our present knowledge of "essential" hypertension.

EDWARD J. HUTH, M.D.

Respiration. Physiologic Principles and Their Clinical Applications. Edited and translated by PETER C. LUCHSINGER, M.D. and KENNETH M. MOSER, M.D. 494 pages; 25.3 × 17.5 cm. The C. V. Mosby Company, St. Louis, 1960. Price, $15.75.

This comprehensive text on cardiopulmonary physiology is a translation of the second edition (1958) of the German text by the same authors. It is divided into four major sections; a discussion of normal respiratory physiology, a description of pulmonary function testing, a discussion of abnormalities of respiratory physiology in general, and the pathophysiology of specific clinical conditions. The authors have covered the fundamentals of clinical pulmonary physiology in a systematic manner, admittedly from the point of view of the Zurich school, which considers arterial blood gas composition to be the most significant parameter of pulmonary ventilation. The book is written more as a reference than as a teaching text. The illustrations are complicated, often being reproductions of experimental records. Many unnecessarily large tables are given. It is full of interspersed historical comments, which certainly add to the interest of the experienced reader, but probably make it more difficult for the newcomer in the field to locate specific information.

Not only is this a good source book, but it presents the viewpoints of this distinguished group to the American audience. The translators have done a creditable job in converting the material into readable English, and have in addition also made real efforts to bridge minor differences between European and American approaches. We are not aware of an equally comprehensive book on this subject in English. However, there are important areas of present interest which are not covered, such as aviation and submarine respiratory physiology, and that of infants and the newborn.

The book is attractive in physical appearance, with a pleasing type face on good paper; the illustrations are clear. The index is good, and the extensive bibliography is up to date.

ROBERT FORSTER, M.D.

The Adrenal Cortex. International Academy of Pathology Monograph. Edited by HENRY D. MOON, M.D. 315 pages; 26 × 18 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York, 1961. Price, $10.50.

This monograph, the third in a series based on conferences held under the auspices of the International Academy of Pathology, has been prepared by nineteen authors. The stated purpose is to provide a "comprehensive reference source." Each section has been written by an acknowledged authority within its sphere. The embryology, normal morphology, pathology, biochemistry, and physiology of the adrenal cortex are considered, along with the relationships of the hypothalamus and the anterior pituitary to adrenocortical function. Methods of analysis for the adrenal secretions, clinical disorders, and treatment are included as well.

Many subjects are treated briefly, by no means comprehensively, and often are inadequately annotated for a reputed reference book. There are occasional inexact interpretations of currently established matters of intermediary steroidal metabolism. These defects raise the question of the imposition placed upon reliable participants in a symposium who are required to detail their presentations. The earnestness of contribution is often of great value in open conference but less apparent in the printed word, and usually the authors have previously published their material in superior fashion elsewhere.

On the other hand, the volume does present a condensation of information, attractively collected in a manner which is easy to read. The morphologic and basic chemical sections are among the best written. In this sense the book may be useful to investigators in allied areas and to others requiring a facile introduction to the subject. The text is amply supplemented with tables and figures. The subject index is thorough. The index of authors is somewhat superfluous since the citations include only a small segment of the literature, often simply reviews. The quality of the paper and the binding are excellent.

ALFRED M. BONGIOVANNI, M.D.

Haemopoiesis: Cell Production and Its Regulation. Editors for the Ciba Foundation, G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P. and MAEVE O'CONNOR, B.A. 490 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1960. Price, $11.00.

This volume of papers on various aspects of hemopoiesis is a direct outgrowth of an international conference on this subject held in London in 1960. First among the subjects covered is the evolution of the lymphomyeloid tissues, with special reference to the use of radioisotope techniques by the Yoffey school. This is followed by the stimulating original studies of the Brookhaven school, using tritiated thymidine, and embodying the important contributions of Cronkite and co-workers. Astaldi's discussion on hemopoiesis and the use of tissue cultures, and Loutit's contribution on transfusion of cells and the resulting type of hemopoiesis are provocative and replete with potential lines of investigation. Granulocytes and erythrocytes come in for a modest share of the discussion in a volume largely devoted to lymphopoiesis and erythropoiesis. Platelets seem to be mentioned only in the section by Linman and Bethell.

Much of the ground covered by this group of papers duplicates that discussed by the Salt Lake City Conference on Cell Proliferation held in January, 1959. There is sufficient added material, however, to make this volume highly valuable to the student and research worker.

L. M. TOCANTINS, M.D.

Textbook of Pathology. An Introduction to Medicine. 7th Ed. By WILLIAM BOYD, M.D., M.R.C.P. 1,370 pages; 26 × 18.5 cm. Lea & Febiger, Philadelphia, 1961. Price, $18.00.

This revision of Dr. Boyd's well-known textbook has provided us with one of the most readable and lucid accounts of human pathology available today. The new edition, like its predecessors, is an outstanding textbook of pathology, and should serve the medical students in the next two or three years as effectively as its earlier editions have done their forerunners in the past.

The first third of the book consists of an outline of general pathology and serves as a concise and comprehensive presentation of the most modern ideas concerning the pathogenesis of disease processes. It could well be used by physicians and others who wish to refresh their ideas in modern terms. It is difficult to choose any one aspect of the section on general pathology for special mention, but perhaps the chapters on ionizing radiation and medical genetics deserve special commendation. Each of these chapters, in the opinion of this reviewer, represents perhaps the most comprehensive short outline of these respective fields now available. The other two-thirds of the book is devoted to regional pathology and is an excellent introduction for medical students to disease processes as they affect the different organs in the human; a physician who wants a simple general review of human pathology will also find these chapters helpful. A difficulty that assails the writer of the textbook on pathology for medical students is to know how much morphological detail to include; Dr. Boyd has judged this with great precision and finished up with a text that has all that the student should know, as well as those things that may not be mandatory but are of interest.

The illustrations are the only feature of the book of which one can be sharply critical; their reproduction is not up to the standard of the text, and they are among the poorest to be seen in any modern textbook of pathology.

Many of them are clearly hardy old servants of Dr. Boyd's earlier texts and ought to have been retired years ago. Apart from the illustrations, the book can be highly recommended to medical students, residents, and practicing physicians as about the best available today.

ASHTON B. MORRISON, M.D.

Progress in Medical Genetics. Volume 1. Edited by ARTHUR G. STEINBERG, Ph.D. 341 pages; 23.5 × 16 cm. Grune & Stratton, Inc., New York, 1961. Price, $9.75.

Eight monographs are collected in the first of what the editor promises will be a series of reviews to be published as advances seem to dictate. The separate contributions are as follows:

James F. Crow: Mutation in man.

J. B. S. Haldane: Natural selection in man.

F. Clarke Fraser: Genetics and congenital malformations.

C. A. Clarke: Blood groups and disease.

Howard Levene and Richard E. Rosenfield: ABO incompatibility.

Donald L. Rucknagel and James V. Neel: The hemoglobinopathies.

Newton E. Morton: Morbidity of children from consanguineous marriages.

Malcolm A. Ferguson-Smith: Chromosomes and human disease.

Haldane, now in Calcutta, introduces his discussion in this fashion:

"I write this chapter under a severe handicap. The nearest library with an adequate coverage on human genetics is in Bombay. I shall therefore miss many important data. Personally, I prefer to live in a country where the assortment of segregating human genes differs from that of Europe and North America to a country with good libraries."

Clarke's introduction is similarly pungent:

"It is reasonable to conclude, from what we know of polymorphism, that individuals belonging to the different blood groups are not equally viable. . . . A valuable line of enquiry which does not yet seem to have been pursued in any detail would be to study the blood group distributions in patients suffering from a wide variety of diseases. It is possible that in some conditions, infectious or otherwise, they would depart from their normal frequencies, indicating that persons of a particular blood group are unduly susceptible to the disease in question" (Ford, 1945).

"I am surprised to see how much space is being wasted in the 'Lancet' and the 'British Medical Journal' on articles dealing with blood group distribution in various diseases . . . knowledge is no substitute for understanding and mathematics is a poor substitute for accurate observations, reliable laboratory work and common sense. The hardest things to explain are those which are untrue" (Wiener, 1956).

From the evidence brought forward in this paper the reader will be able to decide whether the calm predictions of 1945 have been realized. If they have, then the uncompromising prejudices of 1956 are yet another example of the truth that "blind unbelief is sure to err."

The eight reviews are at once authoritative and comprehensive. They should prove enormously useful guides through the rapid developments and voluminous literature of recent years. For example, Rucknagel and Neel state that at least 400 papers on the hemoglobinopathies appeared in 1958 and 1959. In the field of chromosome anomalies, in particular, the availability of up-to-the-semester coverage is useful. Dr. Ferguson-Smith, Dr. Steinberg, and the publisher are to be commended on getting out in June, 1961, a review which covers some communications published less than six months previously.

Dr. David Adlersberg, who died early in 1960, was to be co-editor. The volume is dedicated to him.

The editor is to be congratulated on corraling eight superb reviews. This and the volumes projected for the future will undoubtedly prove useful additions to the medical genetics literature.

VICTOR A. MCKUSICK, M.D.

Book Notices

American Heart Association Monograph. Abstracts 1-1960: Cardiovascular Abstracts, Selected from World Literature. STANFORD WESSLER, M.D., Editor. 192 pages; 26 × 19 cm. American Heart Association, Inc., 44 E. 23rd St., New York 10, N. Y., 1961.

The abstracts in this collection have been selected from among those already published in the *Abstracts* section of *Circulation,* Volumes 21 and 22, and they have been grouped under 22 topical headings. In addition, articles from the same volumes of *Circulation* and from Volume 29 of *Modern Concepts of Cardiovascular Disease* are listed at the end of each topical group. Eighteen reviews of cardiovascular disease are listed at the end of the text. An author index has been included.

EDWARD J. HUTH, M.D.

American Heart Association Monograph. Number Two: Symposium on Coronary Heart Disease. HERRMAN L. BLUMGART, M.D., Editor. 154 pages; 26 × 19 cm. American Heart Association, Inc., 44 E. 23rd St., New York 10, N. Y., 1961.

These papers, which cover selected topics in the pathology, diagnosis, and treatment of coronary artery disease, were originally published in *Circulation* during the last five months of 1960, and in January, 1961.

A subject index appears at the end of the book.

EDWARD J. HUTH, M.D.

Chronic Cor Pulmonale: Report of an Expert Committee. World Health Organization Technical Report Series No. 213. 35 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Available in the U. S. through Columbia University Press, International Documents Service, New York 27, N. Y. Price, $0.30, paper bound.

Studies of the incidence of chronic cor pulmonale in various parts of the world have been handicapped by disagreements and inconsistencies in diagnostic terminology and standards. To clear away these obstacles, a WHO Expert Committee, with Dr. Dickinson Richards as Chairman, compiled a complete classification of cor pulmonale by causative diseases, and a simplified one for the *International Classification of Diseases.*

Most of this brief monograph is concerned with standards for the clinical recognition of chronic cor pulmonale given under these headings: diagnostic indications of right ventricular hypertrophy in pulmonary diseases; definition and diagnosis of pulmonary diseases with special reference to chronic bronchitis and emphysema; the clinical picture of chronic cor pulmonale secondary to pulmonary diseases; and chronic cor pulmonale secondary to vascular diseases.

The Committee also compiled, briefly, their views on treatment and prevention of this disorder and suggested important goals for research.

EDWARD J. HUTH, M.D.

Ileus. Klinik, Radiologie und Therapie. Bibliotheca Gastroenterologica, Fasc. 3. By R. NISSEN and E. HAFTER; H. J. FAHRLANDER, Editor. 112 pages; 25 × 17.5 cm. S. Karger AG, Basel, 1961. Available in the U. S. through Albert J. Pheibig, White Plains, N. Y. Price, $6.00.

Six topics in the problems of ileus are covered in this monograph: diagnosis and differential diagnosis, roentgen diagnosis, electrolyte disturbances, paralytic ileus, techniques and indications for decompression by tube (Miller-Abbott and Cantor), and surgical treatment. The text is entirely in German, but each chapter is summarized in English and French, as well as in German.

These papers were presented September 29 to October 1, 1960, in Zurich, at the twenty-fifth annual meeting of the Swiss Society of Gastroenterology, and the special meeting of the German Society of Gastroenterologia and Metabolic Diseases. A transcript of the discussion which followed these papers at that meeting appears after the last chapter.

EDWARD J. HUTH, M.D.

Tumors of the Female Sex Organs. Part 3. Tumors of the Ovary and Fallopian Tube. (Atlas of Tumor Pathology. Section 1X-Fascicle 33). By ARTHUR T. HERTIG, M.D. and HAZEL GORE, M.B., B.S. 176 pages; 26 × 20 cm. Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D. C. Price, $1.40, paper bound.

This fascicle is well organized and should succeed in eliminating much of the confusion

provoked by this puzzling group of neoplasms. The photography meets the high standards set in the rest of this series. The pathologist will welcome this diagnostic adjunct, and the inclusion of material on treatment and prognosis makes this book a valuable source of reference and review for the clinician.

H. T. ENTERLINE, M.D.

Books Recently Received

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review, but it is not possible to discuss all of them.

The Adrenal Cortex. International Academy of Pathology Monograph. Edited by HENRY D. MOON, M.D. 315 pages; 26 × 18 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York, 1961. Price. $10.50.

Arthropod-Borne Viruses: Report of a Study Group. World Health Organization Technical Report Series, No. 219. 68 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Price, $1.00.

Basic Nursing Education Programmes. A Guide to Their Planning. World Health Organization Public Health Papers No. 7. By KATHARINE LYMAN. 81 pages; 21.9 × 13.9 cm. Compiled by the World Health Organization, Geneva. Available in the U. S. through Columbia University Press, International Documents Service, 2960 Broadway, New York. Price, $1.00, paper bound.

The Cardiac Arrhythmias. A Guide for the General Practitioner. By BRENDAN PHIBBS, M.D. 128 pages; 25.4 × 17.5 cm. The C. V. Mosby Co., St. Louis, 1961. Price, $7.50.

Colloque International sur la Biochemie des Glucides. Structure-Spécificité. Organisé par le Centre National de la Recherche Scientifique avec la Collaboration de la Société de Chimie Biologique. Gif-sur-Yvette, 18–21 Juillet, 1960. Bulletin de la Société de Chimie Biologique, Tome 42, No. 12, 1960. G. CHAMPETIER and R. L. WHISTLER, Présidents du Colloque. 1,901 pages; 24 × 16 cm. Masson et Cie, Paris, 1961. Price, $14.50.

Comparative Epidemiology of the Mental Disorders. Edited by PAUL H. HOCH, M.D. and JOSEPH ZUBIN, Ph.D. 290 pages; 23 × 14.5 cm. Grune & Stratton, Inc., New York, 1961.

Drugs in the Treatment of Disease. Commissioned Articles from the British Medical Journal. Preface by HUGH CLEGG, Editor, British Medical Journal. 516 pages; 22 × 14.5 cm. B.M.A. House, London, 1961. Price, 35 s.

Famous Faces in Diabetes. Compiled by CECIL STRIKER, M.D., with a foreword by ELLIOTT P. JOSLIN, M.D. 256 pages; 26 × 18 cm. G. K. Hall & Co., Boston, 1961. Price, $25.00.

Field Studies in the Mental Disorders. Edited by JOSEPH ZUBIN, Ph.D. 495 pages; 22.5 × 14.5 cm. Grune & Stratton, Inc., New York, 1961.

La Grosse Tuberosite de l'Estomac. Etude Clinique et Radiologique. By T. SCHOPS, with a preface by RENE A. GUTMANN, M.D. 574 pages; 24 × 16 cm. G. Doin & Cie., Paris, 1961. Price, 125 NF.

The Human Adrenal Gland. By LOUIS J. SOFFER, M.D., F.A.C.P., RALPH I. DORFMAN, Ph.D., and J. LESTER GABRILOVE, M.D., F.A.C.P. 591 pages; 24 × 16 cm. Lea & Febiger, Philadelphia, 1961. Price, $18.50.

Hypertension. A Mount Sinai Hospital Monograph. Edited by MILTON MENDLOWITZ, M.D. 156 pages; 26 × 17.5 cm. Grune & Stratton, Inc., New York and London, 1961. Price, $6.50.

Ileus. Klinik, Radiologie und Therapie. Bibliotheca Gastroenterologica, Fasc. 3. By R. NISSEN and E. HAFTER, edited by H. J. FAHRLANDER. 112 pages; 25 × 17.5 cm. S. Karger AG, Basel, 1961. Available in the U. S. through Albert J. Phiebig, White Plains, N. Y. Price, $6.00.

Ionizing Radiation and Health. World Health Organization Public Health Papers No. 6. By Bo LINDELL and R. LOWRY DOBSON. 81 pages; 21.9 × 13.9 cm. Compiled by the World Health Organization, Geneva, 1961. Available in the U. S. through Columbia University Press, International Documents Service, 2960 Broadway, New York 27. Price, $1.00, paper bound.

The Management of the Doctor-Patient Relationship. By RICHARD H. BLUM, Ph.D. 304

pages; 23.5 × 15.7 cm. The Blakiston Division of McGraw-Hill Book Co., Inc., New York, 1960. Price, $8.50.

Medical Examination Review Book. Internal Medicine Current Journal Review. Vol. 7. 194 pages; 21.8 × 15.3 cm. Compiled and published by the Medical Examination Publishing Co., Inc., P.O. Box 36, Fresh Meadows, Flushing 65, N. Y. Price, $6.00.

Medical Pharmacology. Principles and Concepts. By ANDRES GOTH, M.D. 551 pages; 25.3 × 17.5 cm. The C. V. Mosby Co., St. Louis, 1961. Price, $11.00.

Pharmaceutical Advertising. A Survey of Existing Legislation. 53 pages; 24 × 16 cm. Compiled and published by the World Health Organization, Geneva, 1961. Available in the U. S. through Columbia University Press, International Documents Service, 2960 Broadway, New York 27. Price, $0.60, paper bound.

The Premature Baby. 5th Ed. By V. MARY CROSSE, O.B.E., M.D. 266 pages; 21.3 × 14.3 cm. Little, Brown and Co., Boston, 1961. Price, $7.00.

Progress in Medical Genetics. Vol. 1. Edited by ARTHUR G. STEINBERG, Ph.D. 341 pages; 23.5 × 16 cm. Grune & Stratton, Inc., New York, 1961. Price, $9.75.

Public Health Aspects of Low Birth Weight. Third Report of the Expert Committee on Maternal and Child Health. World Health Organization Technical Report Series No. 217. 16 pages; 24 × 16 cm. World Health Organization, Geneva, 1961. Available through Columbia University Press, New York. Price, $0.30, paper bound.

Quinones in Electron Transport. A Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and CECILIA O'CONNOR, B.Sc. 453 pages; 21 × 14.5 cm. Little, Brown and Co., Boston, 1961. Price, $11.00.

Recent Advances in Biological Psychiatry. Edited by JOSEPH WORTIS, M.D. 241 pages; 23.5 × 15.5 cm. Grune & Stratton, New York and London, 1961. Price, $9.75.

Virus Meningo-Encephalitis. Ciba Foundation Study Group No. 7. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MARGARET P. CAMERON, M.A. 120 pages; 19 × 12.5 cm. Little, Brown and Co., Boston, 1961.

MEDICAL NEWS

DEADLINE FOR RECEIPT OF ABSTRACTS

October 15, 1961

43d ANNUAL SESSION—APRIL 9–13, 1962

PHILADELPHIA

Send abstracts 250 words in length, giving titles, authors' names, academic appointments. Original and 5 copies. May be on:

1. **CLINICAL INVESTIGATION**
2. **BASIC MEDICAL SCIENCES as related to Internal Medicine**
3. **CLINICAL STUDIES AND OBSERVATIONS**

Send to: Edward C. Rosenow, Jr., M.D.
Executive Director
AMERICAN COLLEGE OF PHYSICIANS
4200 Pine Street
Philadelphia 4, Pennsylvania

Meetings

Oct. 18–20. Meeting of AHA Council on Arteriosclerosis. The Council on Arteriosclerosis of the American Heart Association will hold its annual meeting at the Hotel Balmoral, Bal Harbour, Miami Beach, Florida, immediately preceding the AHA's annual scientific sessions in the same city, Oct. 20–22. All interested physicians, whether or not they are members of the Council, are invited to attend the sessions. Further information on the Council meeting may be obtained from Dr. Jeremiah Stamler, Chicago Board of Health, 54 West Hubbard St., Chicago 10, Ill., or from the American Heart Association, 44 E. 23rd St., New York 10, N. Y.

Oct. 20–22. American Heart Association—1961 Scientific Sessions. Six sessions on clinical cardiology will be included in the 34th annual scientific sessions of the American Heart Association to be held at the Americana Hotel, Bal Harbour, Miami Beach, Florida. A panel or symposium including related investigative work will be presented at each clinical session. In addition, a total of 18 other scientific sessions will be held concurrently during the three day program. Registration forms, which include applications for hotel reservations, are available from the American Heart Association, 44 E. 23rd St., New York 10, N. Y.

Oct. 22–25. AMERICAN COLLEGE OF GASTROENTEROLOGY, Hotel Cleveland, Cleveland. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.

Nov. 5–8. ASSOCIATION OF MILITARY SURGEONS (68th Annual Convention), Mayflower Hotel, Washington, D. C. Rear Adm. Richard A. Kern, MC, USNR, Ret., 1726 Eye St., N. W., Washington 6, D. C., President.

Nov. 9–11. GERONTOLOGICAL SOCIETY, INC., Penn-Sheraton Hotel, Pittsburgh, Pa. Gerontological Society, Inc., 660 South Kingshighway Blvd., St. Louis 10, Missouri.

INTERNATIONAL AND FOREIGN MEETINGS—1961

Oct. 15–20. FOURTH INTERNATIONAL CONGRESS OF ALLERGOLOGY, Hotel Commodore, New York City. Dr. William B. Sherman, 60 E. 58th St., New York 22, N. Y., Chairman.

Nov. 27–29. AMERICAN SOCIETY OF HEMATOLOGY, Ambassador Hotel, Los Angeles, Calif. Dr. Louis Lowenstein, Royal Victoria Hospital, Montreal, Quebec, President.

Mar. 26–31, 1962. HEALTH AND TUBERCULOSIS CONFERENCE, University College, Ibadan, Nigeria. Conference Secretary, The Chest and Heart Association, Tavistock House North, Tavistock Square, London, W. C. 1.

POSTGRADUATE COURSES

THE AMERICAN COLLEGE OF PHYSICIANS

Schedule of Postgraduate Courses, Fall–Winter, 1961–62

Sept. 18–23, 1961. Course No. 1, CHANGING CONCEPTS OF CARDIOPULMONARY DISEASE, Ohio State University Health Center, Columbus, Ohio; James V. Warren, M.D., F.A.C.P., Director; Joseph M. Ryan, M.D., F.A.C.P., Assistant Director.

Oct. 9–13, 1961. Course No. 2, THE PHYSIOLOGIC BASIS OF INTERNAL MEDICINE, Duke University Medical Center, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., and Elbert L. Persons, M.D., F.A.C.P., Co-Directors.

Nov. 6–10, 1961. Course No. 3, THE INTERNIST'S ROLE IN PREOPERATIVE AND POSTOPERATIVE PROBLEMS, Mayo Clinic, Rochester, Minn.; Hugh R. Butt, M.D., F.A.C.P., and James C. Cain, M.D., F.A.C.P., Co-Directors.

Dec. 4–8, 1961. Course No. 4, ADVANCES IN ELECTROCARDIOGRAPHY, New York University Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director.

Jan. 15–18, 1962. Course No. 5, INTERNAL MEDICINE—TODAY'S PROBLEMS IN DIAGNOSIS AND MANAGEMENT, AND TOMORROW'S PROJECTIONS, Ochsner Foundation Hospital, New Orleans, La.; A. Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors.

Jan. 29–Feb. 1, 1962. Course No. 6, MEDICAL GENETICS, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director.

Feb. 12–16, 1962. Course No. 7, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors.

Feb. 19–23, 1962. Course No. 8, SYMPOSIA ON CHALLENGING MEDICAL PROBLEMS, Baylor University College of Medicine, Houston, Tex.; Raymond D. Pruitt, M.D., F.A.C.P., Director.

For information and application blanks, please write directly to Edward C. Rosenow, Jr., M.D., Executive Director, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

THE ENDOCRINE SOCIETY—NATIONAL INSTITUTES OF HEALTH

Oct. 2–6. THIRTEENTH POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY AND METABOLISM. For information write to Dr. Roy Hertz, National Institutes of Health, Building 10, Bethesda 14, Md. Enrollment limited to 100. Fees, $100.00 for physicians, $30.00 for Residents and Fellows.

NEW YORK UNIVERSITY POSTGRADUATE MEDICAL SCHOOL

Course 563. GYNECOLOGICAL ENDOCRINOLOGY. A full-time, five-day course, October 9 through October 13, 1961, will be given under the direction of Herbert S. Kupperman, M.D. Tuition, $140.00. For further information write Office of the Associate Dean, New York University Postgraduate Medical School, 550 First Avenue, New York 16, N. Y.

THE PHILADELPHIA COUNTY MEDICAL SOCIETY

Oct. 30. The Committee on Nutrition and Metabolism, Philadelphia County Medical Society, jointly with the Division of Behavioral Problems, Department of Health, Common-

wealth of Pennsylvania, and the National Vitamin Foundation, will sponsor a symposium on the problem of alcoholism in the practice of medicine. The symposium will be held at the College of Physicians of Philadelphia, 19 S. 22d Street, Philadelphia, at 2:30 PM.

The Johns Hopkins University School of Hygiene and Public Health

Oct. 31. An informal symposium on "Age Changes in Connective Tissue and Their Clinical Implications" will be held at the New York Academy of Medicine Building, under the auspices of the Institute of Geriatrics of the Home and Hospital of the Daughters of Jacob. The symposium will be divided into two sessions. The morning session will deal with "Biology and Physiology of Connective Tissue," and will be chaired by Nathan W. Shock, M.D., Chief, Gerontology Branch, Department of Health, Education, and Welfare. The afternoon session, "Clinical Implications," will be chaired by Victor McKusick, M.D., Professor of Medicine at The Johns Hopkins Hospital.

University of Southern California

Nov. 9–10. Recent Advances in Medicine, Thurs.–Fri. Statler Hotel, Los Angeles. For information contact Phil R. Manning, Assoc. Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 33.

New York Medical College

Nov. 13–17. The Department of Physical Medicine and Rehabilitation of the New York Medical College will conduct a one-week course for physicians only in "Rehabilitation Care of the Chronically Ill Patient." The course will consist of lectures, seminars, and clinical demonstrations. The teaching staff will include members of the faculty of the medical college, noted guest lecturers, and members of the clinical staff of the hospital center. Tuition: $150. For further information communicate with Raymond C. Lerner, Coordinator, Postgraduate Education, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 E. 105th St., New York 29, N. Y.

American College of Chest Physicians

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses during 1961:

Oct. 23–27. Clinical Cardiopulmonary Physiology. Sheraton-Chicago Hotel, Chicago.

Nov. 13–17. Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases. Park Sheraton Hotel, New York City.

Dec. 4–8. Recent Advances in Diseases of the Chest. Statler-Hilton Hotel, Los Angeles.

Tuition for each course is $75 for members of the American College of Chest Physicians and $100 for non-members. The fee includes attendance at the round table luncheon discussions. For further information write Executive Director, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

Center for Continuation Study, University of Minnesota—Medical Continuation Courses

Jan. 2–6, 1962. Intermediate Electrocardiography for General Physicians and Specialists. For further information write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

Columbia University College of Physicians and Surgeons

March 12–14, 1962. A symposium, "Basic Problems in Neoplastic Disease," will commemorate the Fiftieth Anniversary of the Institute of Cancer Research at Columbia University and the Tenth Anniversary of its affiliated clinical facility, The Francis Delafield Hospital. The symposium is open without fee to all interested workers in this field. For details and applications, write to the Institute for Cancer Research, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York 32, N. Y.

American Psychosomatic Society

The American Psychosomatic Society will hold its nineteenth annual meeting at The Sheraton Hotel, Rochester, N. Y., Friday, Saturday, and Sunday, March 30, 31, and April 1, 1962. The Program Committee welcomes abstracts of original work to be presented at the meeting by members or non-members. Abstracts should be not more than two typewritten pages, and should be submitted in eleven copies. Dead-

line for submission is December 1, 1961. Abstracts should be addressed to the Chairman, 265 Nassau Road, Roosevelt, N. Y.

Examinations and Licensure

American Board of Pediatrics: Written: Jan. 12, 1962. Oral: Atlantic City, April 28–May 1; San Francisco, June 15–18; Chicago, Oct. 6–8; and Pittsburgh, Nov. 30–Dec. 3. Final date for filing application for the written examination is November 30, 1961. Dr. John McK. Mitchell, Rosemont, Pa., Secretary.

American Board of Preventive Medicine: Written examination in public health, aviation medicine, and occupational medicine, Spring of 1962. Dr. Tom F. Whayne, 4219 Chester Ave., Phila. 4, Pa., Secretary.

American Board of Psychiatry and Neurology: Chicago, Oct. 9–10, 1961, and New York, Dec. 11–12. David A. Boyd, Jr., 102–110 Second Ave., S. W., Rochester, Minn., Secretary.

Three-Year Residency in Neoplastic Diseases

The Francis Delafield Hospital, affiliated with Columbia University College of Physicians and Surgeons, New York, offers a three-year residency program accredited by the American Board of Internal Medicine.

The first year includes general medicine consisting of ward service, hematology, cardiology, and diagnostic radiology. The second year includes training in either hematology or cardiology, and supervision of first year residents. The third year may be served as the Chief Resident or in a Fellowship program. Opportunity to do clinical and laboratory investigations is available during the second and third years.

The program can be started July 1, 1962. The stipend depends upon individual experience, minimum, $3,380, and living quarters are provided in the hospital. Applications should be addressed to Alfred Gellhorn, M.D., Director of Medicine, Francis Delafield Hospital, 99 Fort Washington Ave., New York 32, N. Y.

Medical Periodicals for the World Medical Association

The World Medical Association is requesting that American physicians help to provide medical periodicals and books to foreign libraries, medical groups, and hospitals. It is requested that interested physicians provide the W. M. A. with the names of the periodicals which they are willing to send regularly overseas. Wrappers addressed to a foreign physician in need of a particular publication will be furnished the donor. For further information please write World Medical Association, U. S. Committee, Inc., 10 Columbus Circle, New York 19, N. Y.

Fourth Annual MMM Awards for Medical Writing

The Editors of *Modern Medical Monographs* announce the 1961 competition for unpublished manuscripts on clinical subjects in the field of internal medicine. The purpose of these annual awards, which are known as the *Modern Medical Monographs* Awards, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing.

The first prize is $500. In addition, the authors of other top-ranking manuscripts which are found suitable will be offered a contract for publication of their work as a book in the series *Modern Medical Monographs* under standard royalty arrangements. The generosity and cooperation of Dr. Henry M. Stratton, President, Grune & Stratton, Inc., publishers of the series, have made these awards possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association, and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monographs*.

Following are the rules of the competition:

1. The author must be a graduate physician, less than 40 years of age.

2. Manuscripts (including illustrations, if any) should be submitted in duplicate (original and one copy) by registered mail, postmarked no later than December 1, 1961, to Irving S. Wright, M.D., 450 East 69th Street, New York 21, N. Y.

3. The manuscript, including the bibliography, must consist of not less than 130, or more

than 200, double-spaced typewritten pages with one-inch margins, and not more than 30 illustrations (pictorial charts, drawings, diagrams, or photographs).

4. Fishbein's book, *Medical Writing* (3rd Ed.), should be followed in preparation of the manuscript, use of abbreviations, etc., and bibliographic form.

Institute for Aging Research Proposed

The medical research section of the White House Conference on Aging in Washington, D. C., has recommended the establishment of an Institute of Aging Research within the National Institutes of Health. This would be the eighth institute at NIH and would probably cost in the vicinity of $20,000,000 to establish.

INSTRUCTIONS TO AUTHORS

MANUSCRIPTS: All papers should be typewritten on one side of the paper and double spaced (including references, figure legends, and footnotes). The original and one carbon copy should be submitted with duplicate copies of all figures and tables. A separate title page should include the following: title, subtitle (if any), author(s) and his (their) degree(s), F.A.C.P. (if Fellow of the American College of Physicians), city or town where the work was done, hospital or academic institution (if any), and necessary acknowledgment of financial sponsors.

The introduction should orient the paper in relation to its field and should state its purpose. The main sections (for example, RESULTS) should be identified by centered headings in capital letters. Indicate further subdivisions by side headings that are flush with the left-hand margin and one line above the text, and/or by paragraph headings which should be indented on the first line of the paragraph and underlined. Extensive discussion should be separated from the presentation of the results. A succinct summary should state what was done, what was found, and what the findings are interpreted to mean. For guidance to sound grammar and clear style consult *The Elements of Style* by W. Strunk, Jr. and E. B. White, The Macmillan Co., New York, 1959.

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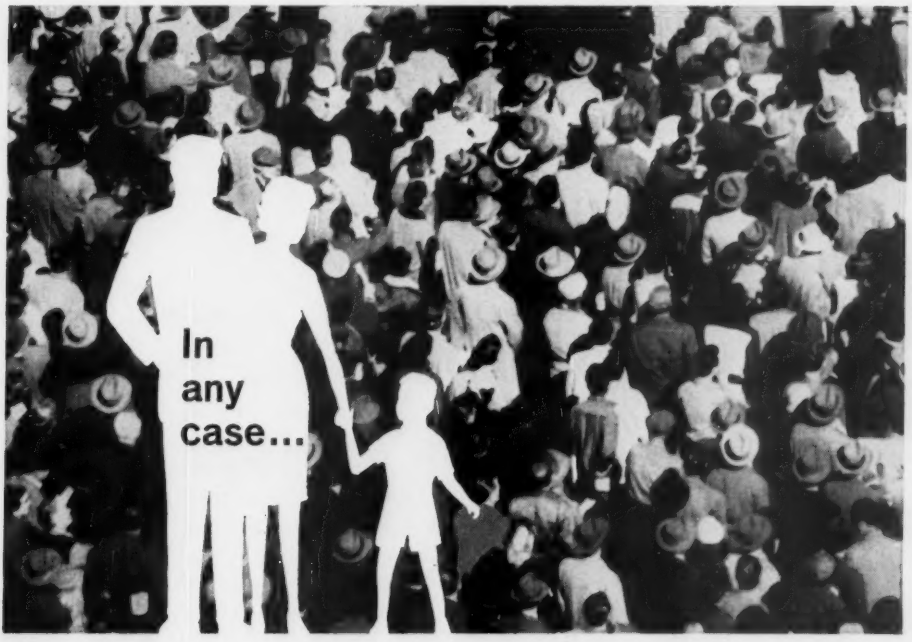
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ABBREVIATIONS

intramuscular	im	centigrade	C	millimeter	mm	volume	vol
intraperitoneal	ip	Fahrenheit	F	centimeter	cm	milliliter	ml
intravenous	iv	specific gravity	sp gr	meter	m	liter	liter
subcutaneous	sc	hemoglobin	Hb	cubic millimeter	mm^3	concentration	concn
by mouth	po	pressure of CO_2	P_{CO_2}	square meter	m^2	microequivalent	μEq
min. lethal dose	MLD	number	no.	weight	wt	milliequivalent	mEq
unit	U	standard deviation	SD	microgram	μg	millimolar	mM
international unit	IU	standard error	SE	milligram	mg	milliosmole	mOsm
minute	min	probability	*P*	gram	g	milligram per cent	mg per 100 ml
calorie (small)	cal	correlation coefficient	R	kilogram	kg		

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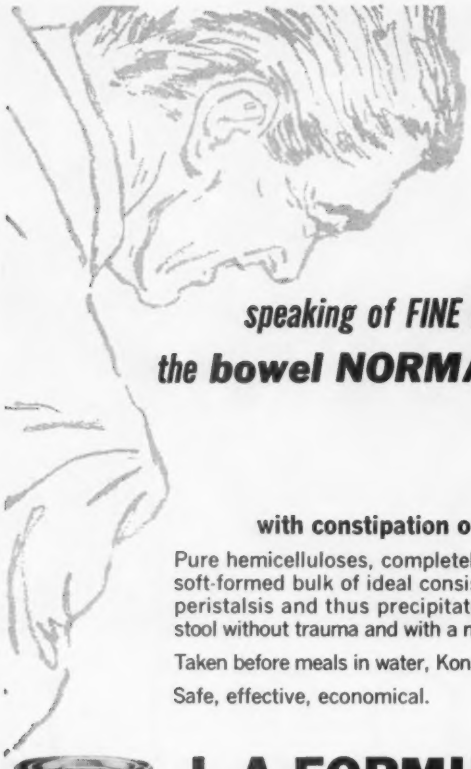
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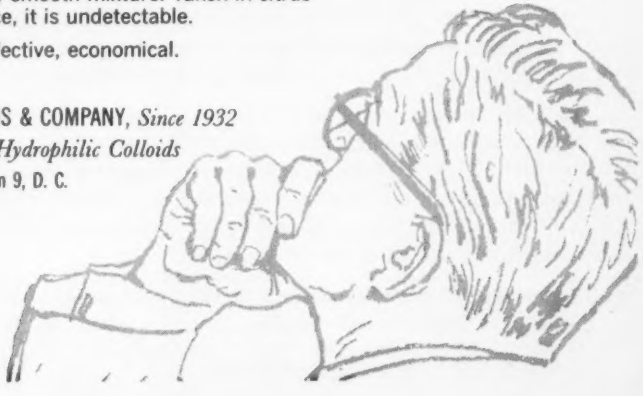
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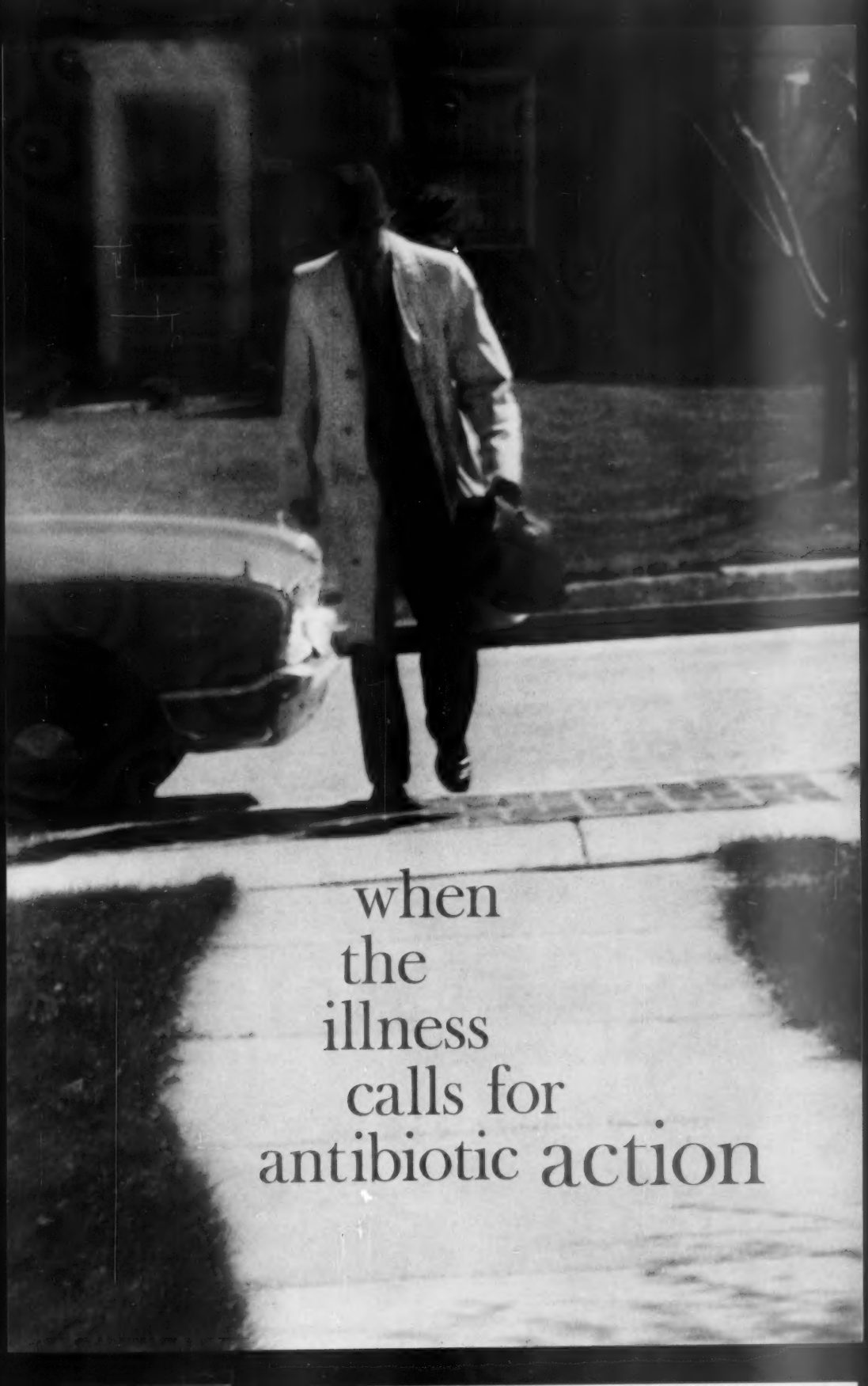
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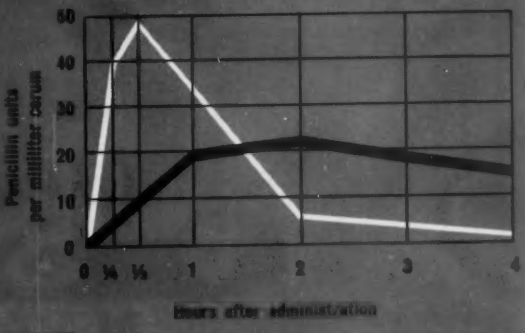
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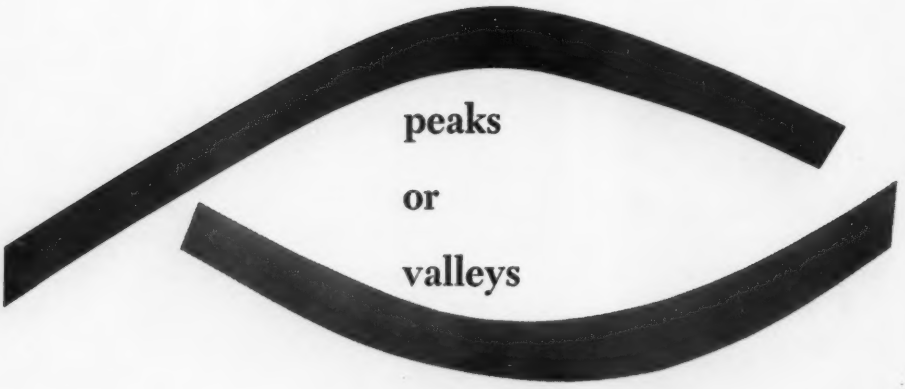
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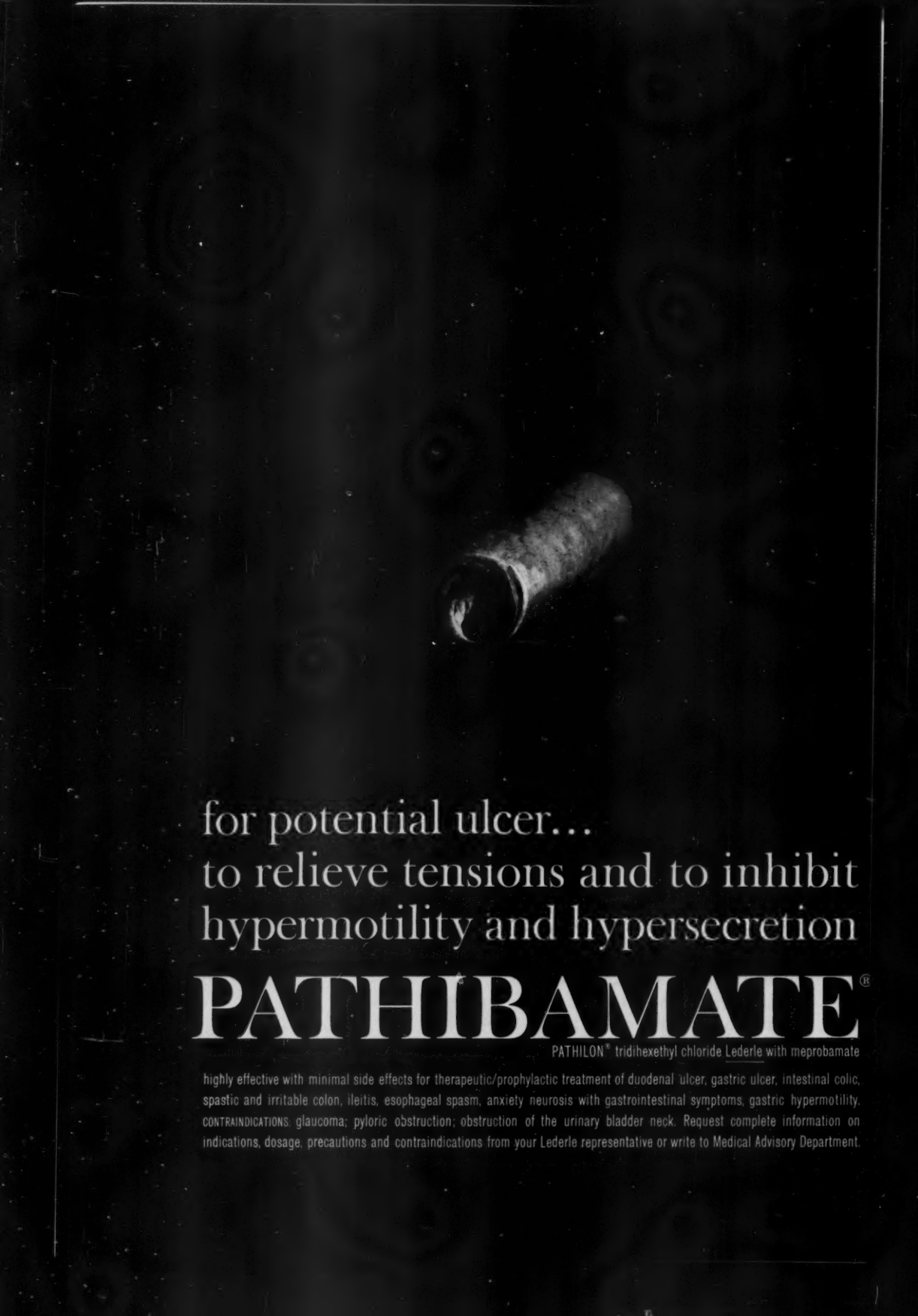
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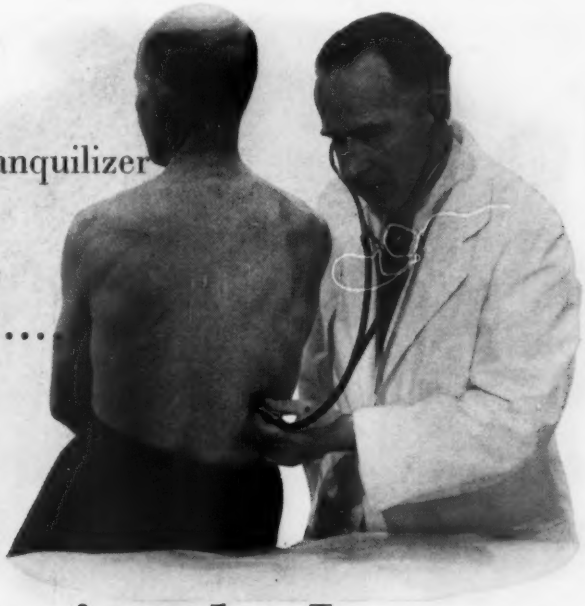
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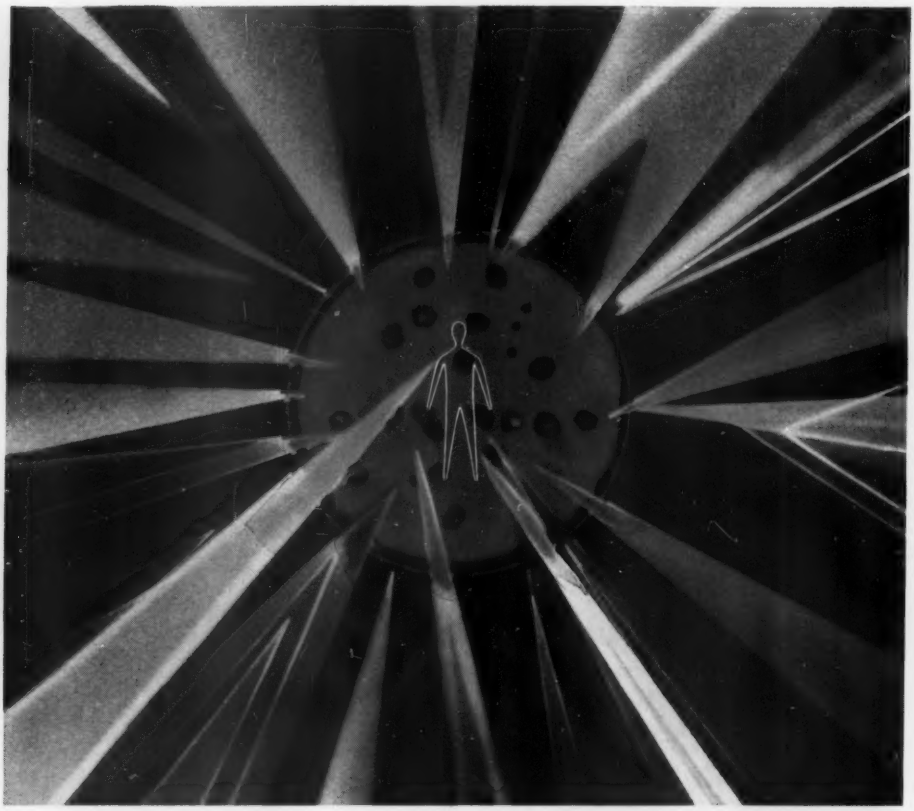
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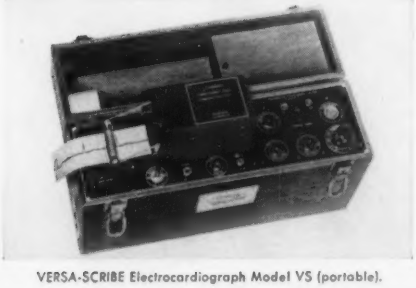
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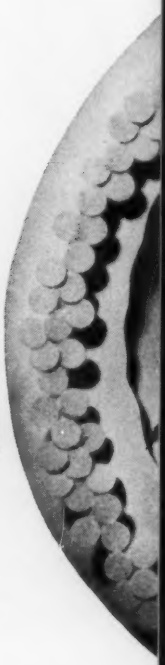
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(1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956.

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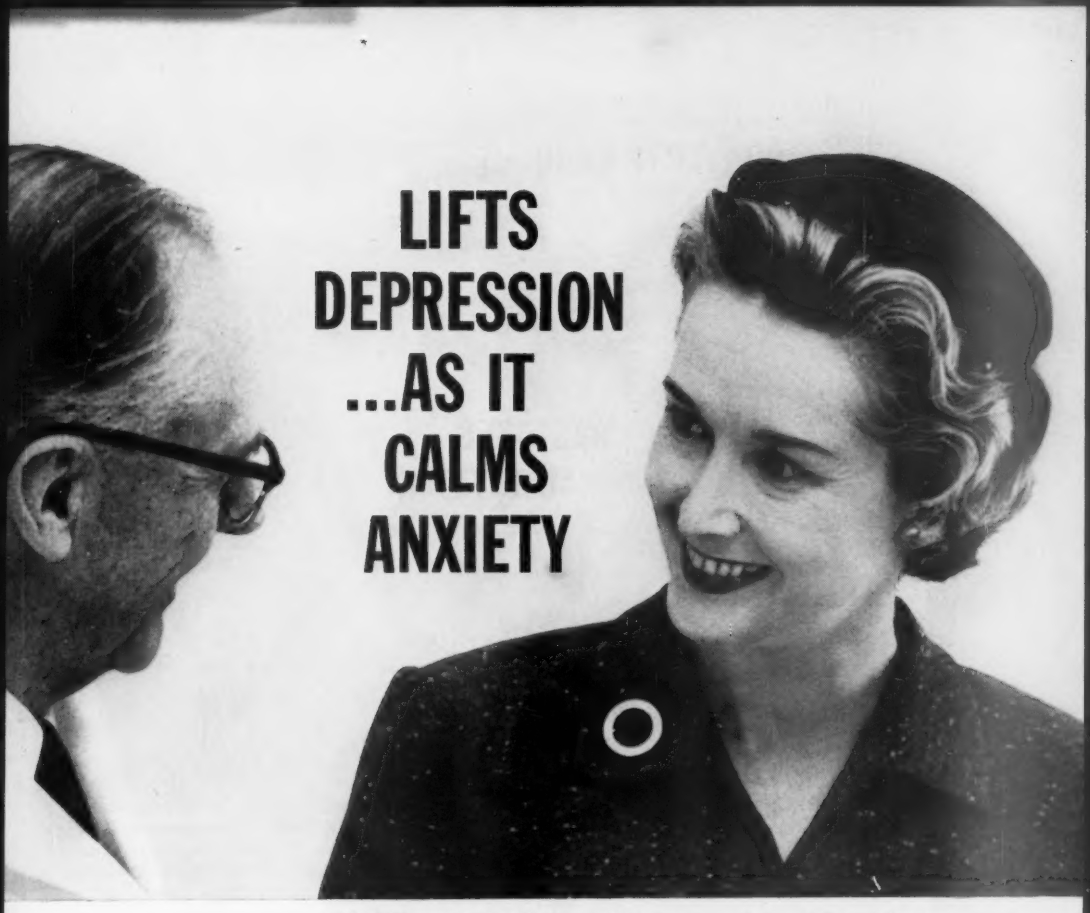
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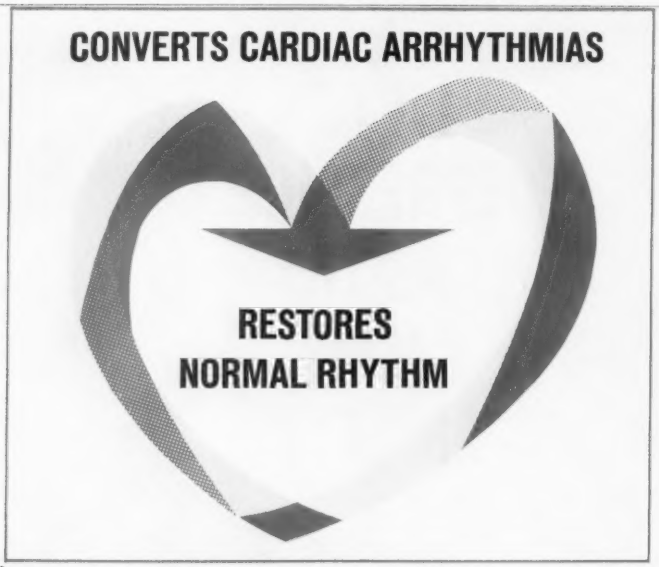
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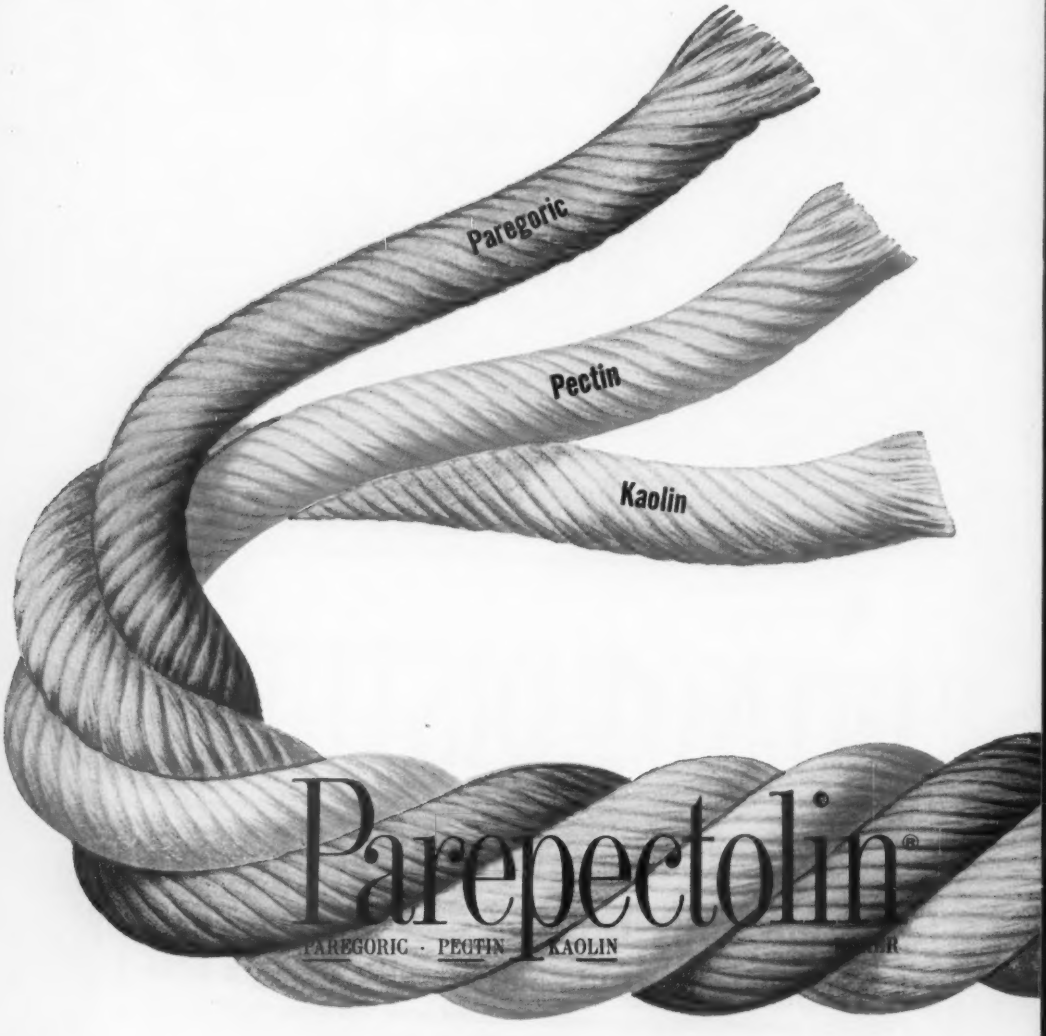
REFERENCES: **1.** Shaftel, N., Halpern, A.: Am. J. Med. Sci. 236:184 (Aug.) 1958. **2.** Sokolow, M., Edgar, A. L.: Circulation 12:576, 1950. **3.** Bellet, S., Finkelstein, D., Gilmore, H.: A.M.A. Arch. Int. Med. 100:750 (Nov.) 1957. **4.** Schwartz, G.: Angiology 10:115 (April) 1959. **5.** Tricot, R., Nogrette, P.: Presse med 68:1085 (June 4) 1960.

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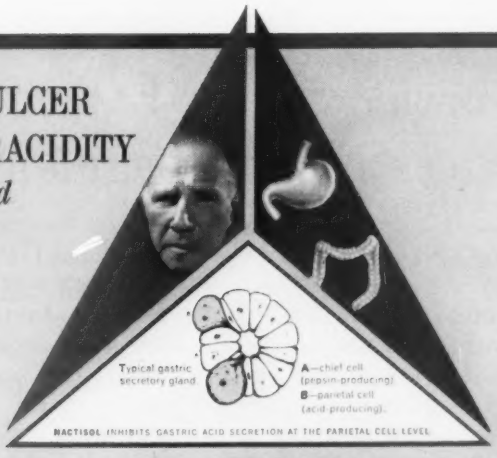
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References

1. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (December) 1958. 2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. *26*:502-509 (October) 1959. 3. Steigmann, F.: Clinical Report to McNeil Laboratories. 4. Lorber, S. H.: Clinical Report to McNeil Laboratories, December 6, 1960. 5. Rider, J. A.: Clinical Report to McNeil Laboratories.

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No. 1 **of a series reporting on Endo Laboratories' Anticoagulant Survey**

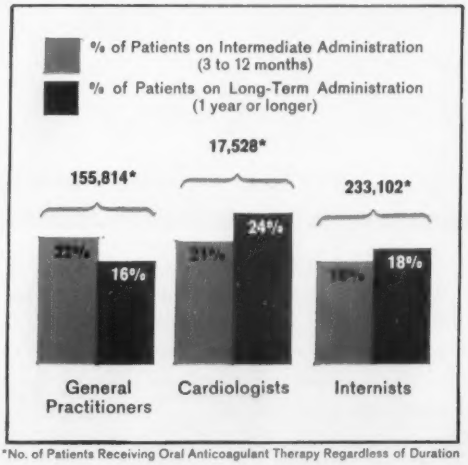
Nationwide Survey Explores Current Practices in Anticoagulant Therapy

Early in 1961 Endo Laboratories undertook a comprehensive survey of physicians' attitudes toward oral anticoagulants and their application in daily practice. Approximately 90,000 physicians received a questionnaire which covered such basic matters as *when, how,* and *for what periods* anticoagulants were used, the *specific advantages* of the agent most often selected by general practitioners, internists, and cardiologists, *factors* relating to the effective, safe administration of anticoagulants, and other pertinent areas of clinical interest. A total of 10,016 physicians completed and returned the *Anticoagulant Survey.*

The vast accumulation of data has now been analyzed and tabulated so that one can draw conclusions regarding the actual practice of thousands of physicians. Endo is happy to present the findings of *Anticoagulant Survey* in the first of a series of brief reports. It is our purpose thereby to contribute to a better understanding of the use of anticoagulants, therapeutically and prophylactically. We would greatly appreciate your comments and observations on this series. For more detailed information on *Anticoagulant Survey,* write to the Professional Service Dept., Endo Laboratories, Richmond Hill 18, New York.

Long-Term Anticoagulant Therapy of Myocardial Infarction More Widely Accepted

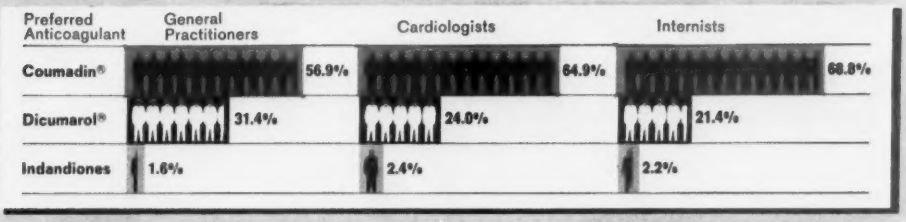
Broad clinical experience[1-12] has indicated the value of oral anticoagulants in preventing or minimizing the occurrence of myocardial infarctions and extending life expectancy, particularly on long-term use. Reports from general practitioners and specialists reveal that these life-saving agents are being used *prophylactically* not only after frank myocardial infarction but also in *impending* infarction associated with angina pectoris. The following table shows the percentage of patients who have been maintained on oral anticoagulant therapy for extended periods of time, according to replies of physicians who answered the Endo anticoagulant questionnaire.



*No. of Patients Receiving Oral Anticoagulant Therapy Regardless of Duration

Specialists and General Practitioners Using Coumadin Increasingly

A comparison of Coumadin (warfarin sodium), Dicumarol (bishydroxycoumarin), and Indandiones showed that coumarin derivatives were prescribed most often and that Coumadin was the drug of choice by a wide margin.



It is noteworthy that 80% of the general practitioners, 80% of the internists, and 86% of the cardiologists favoring Coumadin reported their use of oral anticoagulants to be **increasing.** Of 3,092 responding physicians in general practice, 564 had had patients on Coumadin for one year, 628 for two years, 479 for three years, 215 for four years, 181 for five years, and 149 for **more than five years.**

Specialists Favor Tapering Anticoagulant Dosage Before Discontinuance

Abrupt cessation of anticoagulant therapy, especially after long-term administration, has been cautioned against by some clinicians[5,12] because of the possibility of a consequent state of *hypercoagulability* with increased risk of thromboembolism. *Anticoagulant Survey* showed that of the general practitioners who stated their procedure more than half did *not* taper the dose before discontinuance; on the other hand, a majority of internists and cardiologists did taper the dose over several weeks.

Periodic Prothrombin Time Tests Essential to Effectiveness and Safety

Especially in long-term therapy, *periodic prothrombin time determinations* are recognized as vital to effectiveness and safety. Most of the reporting physicians are having these tests performed at one-week, two-week, or four-week intervals. The following data from *Anticoagulant Survey* indicate that the predominant trend is toward testing at intervals of two weeks or longer, and that this procedure is observed by a significantly higher percentage of reporting physicians who prefer Coumadin than by those who favor Dicumarol.

Preferred Anticoagulant	PT Tests Every Week		PT Tests Every 2 to 4 Weeks or Longer	
	GP's	Specialists	GP's	Specialists
Coumadin	17%	18%	63%	67%
Dicumarol	27%	23%	55%	60%

The preferred prothrombin time range was between 1½ to 2½ times normal control; the most favored prothrombin time was twice normal, or 26 seconds. (Complications of anticoagulant therapy will be discussed in a subsequent report.)

Physicians Stress Predictability and Ease of Maintenance in Selecting Anticoagulant

In characterizing the *advantages* of the oral anticoagulant most often prescribed (Coumadin), general practitioners, cardiologists, and internists were unanimous in listing, in order of importance: (1) *more predictable effect,* (2) *easier maintenance,* and (3) *single daily dose.* Among Dicumarol prescribers, on the other hand, "single daily dose" was first in importance, "more predictable effect" second, and "easier maintenance" third.

These data confirm the unusually consistent recognition of Coumadin advantages which have made possible a smoother, more easily managed long-term anticoagulant regimen. Since Coumadin may be given I.M. and I.V. as well as orally, it is also the most versatile of anticoagulants in hospital or office practice.

References: 1. Thomes, A. B., et al.: J.A.M.A. 176:181, 1961. 2. Nora, J. J.: **Ibid.** 174:118, 1960. 3. **Idem:** M. Times 89:502, 1961. 4. Beamish, R. E., and Storrie, V. M.: Heart Bull. 10:41, 1961. 5. Nichol, E. S., et al.: Am. Heart J. 55:142, 1958. 6. Manchester, B.: Ann. Int. Med. 47:1202, 1957. 7. Report of Working Party on Anticoagulant Therapy in Coronary Thrombosis to M. Res. Council: Brit. M. J. 1:803, 1959. 8. Friedberg, C. K.: New York J. Med. 58:877, 1958. 9. Seaman, A. J.: GP 22:135, No. 4, 1960. 10. Stephens, C. A. L., Jr.: Arizona Med. 17:499, 1960. 11. Canady, E. W., et al.: Illinois M. J. 113:50, 1958. 12. Littman, M. L.; Barrett, E. A., and Shapiro, S.: Scientific Exhibit, 110th Annual Meet., A.M.A., New York, N. Y., June 25-30, 1961.

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The Committee on Program Desires Original Contributions Concerning:

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1. Selzer, A., and Rytand, D. A.: COUNCIL ON DRUGS, Report to the Council, J.A.M.A. 168:762, (Oct. 11) 1958.

2. Weil, M. H.: J.A.M.A. 171:1868, (Nov. 28) 1959.

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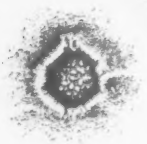
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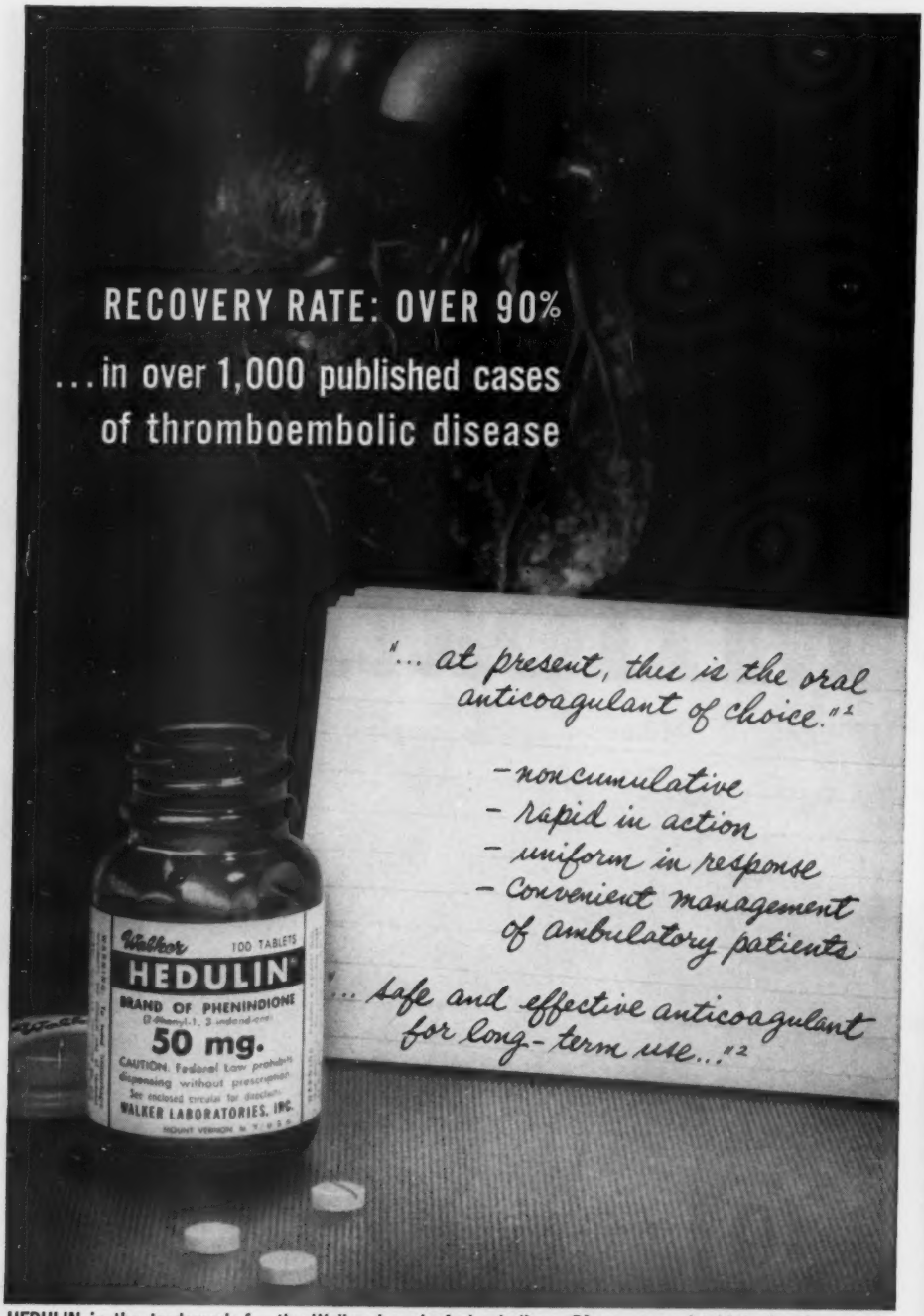
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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	18–22	25–29	2–6	9–13	16–20	23–27	Oct. 30–Nov. 3	6–10	13–17	20–24	Nov. 27–Dec. 1	4–8	11–15	18–22	25–29	1–5	8–12	15–19	22–26	Jan. 29–Feb. 2	5–9	12–16	19–23
Course No. 1, CHANGING CONCEPTS OF CARDIOPULMONARY DISEASE, Ohio State University Health Center, Columbus, Ohio; James V. Warren, M.D., F.A.C.P., Director; Joseph M. Ryan, M.D., F.A.C.P., Assistant Director.	18–23																						
Course No. 2, THE PHYSIOLOGIC BASIS OF INTERNAL MEDICINE, Duke University Medical Center, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., and Elbert L. Persons, M.D., F.A.C.P., Co-Directors.				X																			
Course No. 3, THE INTERNIST'S ROLE IN PREOPERATIVE AND POSTOPERATIVE PROBLEMS, Mayo Clinic, Rochester, Minn.; Hugh R. Butt, M.D., F.A.C.P., and James C. Cain, M.D., F.A.C.P., Co-Directors.								X															
Course No. 4, ADVANCES IN ELECTROCARDIOGRAPHY, New York University Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director.												X											
Course No. 5, INTERNAL MEDICINE—TODAY'S PROBLEMS IN DIAGNOSIS AND MANAGEMENT, AND TOMORROW'S PROJECTIONS, Ochsner Foundation Hospital, New Orleans, La.; A. Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors.																		15–18					
Course No. 6, MEDICAL GENETICS, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director.																				29–1			
Course No. 7, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors.																						X	
Course No. 8, SYMPOSIA ON CHALLENGING MEDICAL PROBLEMS, Baylor Univ. College of Medicine, Houston, Tex.; Raymond D. Pruitt, M.D., F.A.C.P., Director.																							X

Please Mention this Journal when writing to Advertisers


Increasingly...
the
trend is to
Terramycin®
BRAND OF OXYTETRACYCLINE
confirmed dependability in upper respiratory tract infections is just one reason why

Jacques and Fuchs* recently reported on experience with Terramycin in 106 patients with a variety of acute and chronic upper respiratory tract infections, many of which had failed to respond to other antibiotics. Oral dosage was preceded by intramuscular injection in 44 cases. "It was the impression of the hospital staff that oxytetracycline [Terramycin] was not only better tolerated, but more effective than other antibiotics habitually used."

The investigators noted that "some of the best results were seen in patients who were most severely ill."

According to the authors, the availability of Terramycin as a preconstituted intramuscular solution makes it feasible "to treat serious infections with a broad-spectrum antibiotic that has rapid action, and to continue with the same antibiotic given orally as soon as the infection is brought under control."

The results reported in this and many other studies confirm the vitality of Terramycin for broad-spectrum antibiotic therapy and demonstrate why—increasingly—the trend is to Terramycin.



In brief

The dependability of Terramycin in daily practice is based on its broad range of antimicrobial effectiveness, excellent toleration, and low order of toxicity. As with other broad-spectrum antibiotics, overgrowth of nonsusceptible organisms may develop. If this occurs, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing. Glossitis and allergic reactions to Terramycin are rare. As with all I.M. preparations, injection should be made within the body of a relatively large muscle. Care should always be taken to avoid injection into a major nerve or its surrounding sheath. For complete dosage, administration, and precaution information, read package insert before using.

More detailed professional information available on request.

Terramycin®

BRAND OF OXYTETRACYCLINE

INTRAMUSCULAR SOLUTION

50 mg./cc. in 10 cc. vials; 100 mg. and 250 mg. in 2 cc. ampules

the broad-spectrum antibiotic ready for immediate intramuscular injection . . . conveniently preconstituted . . . notably well tolerated at injection site with low tissue reaction compared to other broad-spectrum antibiotics

another reason why the trend is to Terramycin—*versatility of dosage form:*

TERRAMYCIN Capsules
250 mg. and 125 mg. per capsule—for convenient initial or maintenance therapy in adults and older children

TERRAMYCIN Syrup / Pediatric Drops
125 mg. per tsp. and 5 mg. per drop (100 mg./cc.), respectively—deliciously fruit-flavored, preconstituted aqueous suspensions

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PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc.
New York 17, N. Y.

*Jacques, A. A., and Fuchs, V. H.: J. Louisiana M. Soc 113:200, May, 1961.

Pfizer *Science for the world's well-being®*

Dear Doctor:

Reports from our representatives indicate that many physicians would appreciate simplification for prescription-writing purposes of the names of Terramycin products in both the "plain" and the "Cosa" dosage forms.

The "Cosa" forms originated, you may recall, on the basis of clinical evidence of enhanced antibiotic absorption when glucosamine is employed in oral administration. To permit each physician individually to study this evidence and choose which form he would prefer to prescribe, we offered Terramycin in both forms—that is, in the regular Terramycin forms without glucosamine, and in the "Cosa" forms with glucosamine.

This distinction appears to be no longer necessary since glucosamine, a highly acceptable excipient for oral antibiotics, now is being incorporated uniformly in all such forms, thereby simplifying nomenclature and your prescription writing.

Accordingly, and effective immediately, forms incorporating glucosamine will be offered simply as Terramycin without the "Cosa" prefix.

To make clear just which forms are affected, please refer to the brief tabulation (below) of Terramycin dosage forms both *before* and *after* this change. We are also requesting our representative to call on you at an early date to answer any questions that may arise.

We feel certain that this action, prompted by your comments and those of many other physicians, will simplify your writing of prescriptions for Terramycin products.

We welcome your comments on this action and on any other phase of our operations, since it is our objective to render every service as efficiently as possible to our friends in the medical profession.

Sincerely,
PFIZER LABORATORIES

The following table indicates the former name and the current name of Terramycin systemic preparations:

FORMERLY NAMED	NOW NAMED
Cosa-Terramycin® Capsules	**Terramycin**® Capsules*
Cosa-Terrabon® Oral Suspension	**Terramycin** Syrup
Cosa-Terrabon Pediatric Drops	**Terramycin** Pediatric Drops

and simpler names for these Terramycin-containing formulations:

Cosa-Terrastatin® Capsules	**Terrastatin**® Capsules
Cosa-Terrastatin for Oral Suspension	**Terrastatin** for Oral Suspension
Cosa-Terracydin® Capsules	**Terracydin**® Capsules

. . . and these names remain unchanged:
Terramycin Intramuscular Solution
Terramycin Intravenous

**Terramycin Capsules* without glucosamine *are no longer available.*

The clinical versatility of Terramycin is enhanced by its specialized dosage forms adapted to individual needs—*another reason for the trend to Terramycin.*



Naturetin releases the pent-up flood

When fluid "backs up" in the body, as it does in edematous states, Naturetin, an "...extraordinarily effective diuretic...,"[1] serves to remove fluid excess.

The diuretic effect on the patient is dramatic. Usually, the blood pressure of normotensive patients remains unaffected. Naturetin has no apparent influence of clinical importance on serum electrolytes,[2] and it causes a relatively small increase in the urinary pH.[3]

For the next patient you see with evidence of fluid retention, prescribe Naturetin and observe how the floodgates open and release the excess fluid. The average dose is a single 5 mg. tablet daily; to initiate therapy, doses up to 20 mg. may be given once daily or in divided doses.

Supply: Naturetin Tablets, 5 mg., scored, and 2.5 mg. Naturetin ℰ K (5 ℰ 500) Tablets, capsule-shaped, containing 5 mg. bendroflumethiazide and 500 mg. potassium chloride. Naturetin ℰ K (2.5 ℰ 500) Tablets, capsule-shaped, containing 2.5 mg. bendroflumethiazide and 500 mg. potassium chloride.

References: 1. David, N. A.; Porter, G. A.; and Gray, R. H.: Monographs on Therapy *5*:60 (Feb.) 1960. 2. Fuchs, M.; Moyer, J. H.; and Newman, B. E.: Op. cit. *5*:55 (Feb.) 1960. 3. Ford, R. V.: Current Therap. Res. *2*:92 (Mar.) 1960.

For full information, see your Squibb Product Reference or Product Brief.

Naturetin Squibb Bendroflumethiazide

Naturetin℮K Squibb Bendroflumethiazide with Potassium Chloride

SQUIBB *Squibb Quality—the Priceless Ingredient*

'NATURETIN'® IS A SQUIBB TRADEMARK.

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new Tandearil® Geigy

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a new development in nonhormonal, anti-inflammatory therapy

more specific than steroids—
Acts directly on the inflammatory lesion **without** altering pituitary-adrenal function . . . **without** impairing immunity responses.[8-11]

more dependable than enzymes—
Rapid and complete absorption, without the uncertainty of oral or buccal enzyme therapy.[5]

more potent than salicylates—
Anti-inflammatory potency of Tandearil markedly superior to aspirin.[12]

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1,2,3]; gout[1,4,5]; acute superficial thrombophlebitis[6,7]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,4]; severe forms of a variety of local inflammatory conditions[8,9,10].

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing. Full product information available on request.

availability:
Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

references:
1. Graham, W.: Canad. M.A.J.: 82:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Klem, I. M.: Arth. and Rheumat. 2:212, 1959. 3. O'Reilly, T. J.: J. Irish M.A. 46:106, 1960. 4. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 98:31, 1959. 5. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 6. Stein, I. D.: Ann. N.Y. Acad. Sc. 86:307 (March 30) 1960. 7. Barczyk, W., and Röth, W.: Praxis 49:589, 1960. 8. Miller, J. M., et al.: Antibiotic Med. and Clin. Therapy 7:645, 1960. 9. Domenjoz, R., Jr., and Rousselot, L. M.: Am. J. Surg. 97:429, 1959. 10. Summary of individual case histories submitted to Geigy. 11. Domenjoz, R.: Ann. N.Y. Acad. Sc. 86:263, 1960. 12. Smyth, C. J.: Ann. N.Y. Acad. Sc. 86:292, 1960.

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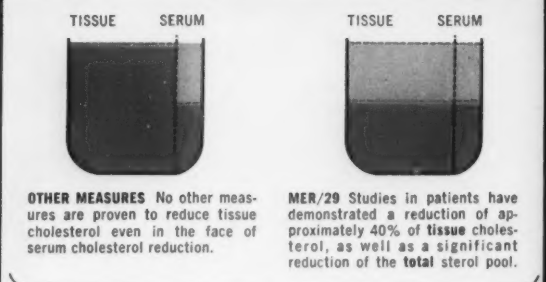
after 3 years' clinical experience:
here is what we now know about MER/29 and

We know that MER/29 lowers cholesterol in 8 out of 10 patients, even without dietary restrictions. In 576 patients studied by various physicians, average cholesterol levels dropped from 303 mg. % to 241 mg. % — an average decrease of 62 mg. %.

We know that MER/29 reduces total sterols in both blood and tissue.

We know that MER/29 does this by inhibiting the body's own production of cholesterol.

We know that its use in over 300,000 patients re-affirms the safety margins established in early laboratory and clinical data.



OTHER MEASURES No other measures are proven to reduce tissue cholesterol even in the face of serum cholesterol reduction.

MER/29 Studies in patients have demonstrated a reduction of approximately 40% of **tissue** cholesterol, as well as a significant reduction of the **total** sterol pool.

effect on
body pool of cholesterol

We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

decreased incidence and severity of anginal attacks
improved ECG patterns
diminished nitroglycerin dependence
increased sense of well-being

"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris."
—*Hollander, W.*, et al.: *J.A.M.A.* 174:*5 (Sept. 3) 1960.*

"Nitroglycerin requirements decreased in 3 [of 5 out-patient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations."
—*Corcoran, A. C.*, et al.: *Progr. Cardiovasc. Dis. 2:(Pt. 1) 576 (May) 1960.*

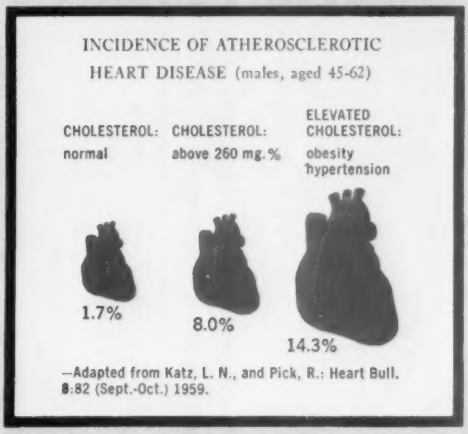
"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina."
—*Lisan, P.: Progr. Cardiovasc. Dis. 2:(Pt. 1) 618 (May) 1960.*

. . .what we are learning about atherosclerosis

It has become generally accepted that elevated lood cholesterol or lipid, if sustained long nough, leads to early atherosclerosis."
Page, I. H.: Mod. Med. 29:71 (Mar. 20) 1961.

pidemiologic studies show that low cholesterol evels are associated with low incidence of therosclerosis and coronary artery disease.

n the basis of such studies, Stamler has said: ...a 15 to 20 per cent reduction in mean serum holesterol levels alone might be associated with 25 to 50 per cent reduction in coronary disase incidence rates in middle-aged men."
Stamler, J.: Am. J. Pub. Health 50:(Pt. 2) 14 Mar.) 1960.



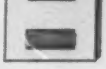
Despite our knowledge of the action, benefits nd safety of MER/29, much remains to be iscovered about the basic concept of choles- erol-lowering therapy. In this, MER/29 is omparable to the well-accepted use of anti- ypertensive agents: we know they lower blood ressure, but we cannot prove that lowering lood pressure will also lower morbidity or mor- ality. Yet few physicians hesitate to use these gents. The possible good is too great to ignore.

o it is with MER/29. No one can yet be certain hat sustained lowering of total body sterols will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

Perhaps that is why an increasing number of physicians are now prescribing MER/29. They wish to assure their hypercholesterolemic, coronary artery disease, and atherosclerotic patients this reasonable hope.

It is a decision facing every physician.

Complete bibliography and prescription information on request.



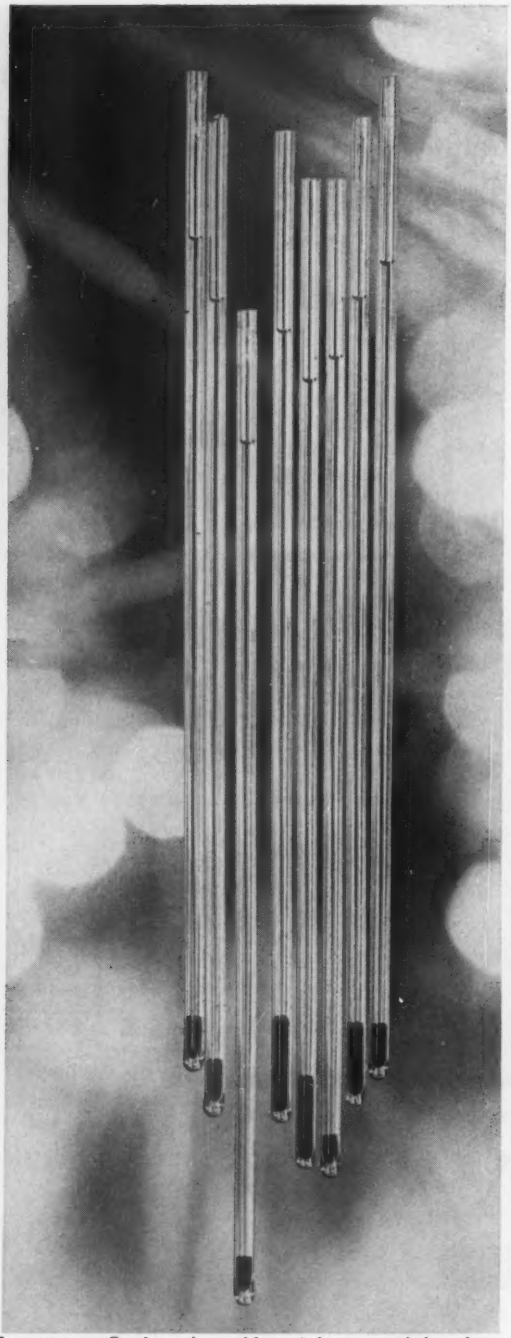
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(triparanol)

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The Wm. S. Merrell Company
Division of Richardson-Merrell Inc.
Cincinnati, Ohio/ Weston, Ontario

TRADEMARK: MER/29®



IMMUNOCRIT® tubes, pictured here 4 times actual size, show results of centrifuging patients' serums with BETA-L TEST antiserum. Longest columns of precipitate indicate high beta-lipoprotein levels.

NEW...

A SPECIFIC SIMPLE INEXPENSIVE TEST FOR ESTIMATING SERUM BETA-LIPOPROTEIN LEVELS

BETA-L TEST™

The growing evidence implicating beta-lipoprotein as one of the agents responsible for atherosclerosis has emphasized the need for a test procedure which is reliable, yet simple enough to be suited to clinical purposes.[1] Hyland BETA-L TEST answers this need. BETA-L TEST results show a close correlation with complex quantitative methods now in use, yet BETA-L TEST can be performed in ten minutes on one drop of serum and employs a minimum of laboratory equipment and technical skill.[2]

The resulting economy and simplicity provide you with a reliable routine screening test and make frequent serial determinations of beta-lipoprotein practical for the first time.

When ordering your next beta-lipoprotein determinations, specify Hyland BETA-L TEST. Materials for BETA-L TEST are now available to your laboratory in 60-test kits.

1. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, Am. Pract.–Dig. Treat. *12:* 235 (April) 1961.
2. Heiskell, C. L., Fisk, R. T., Florsheim, W. H., Yachi, A., Goodman, J. R., and Carpenter, C. M.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222 (March) 1961.

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for controlled therapeutic nutrition

during hospitalization and throughout convalescence

SUSTAGEN®

Complete therapeutic nutriment

to supply all or part of the patient's nutritional requirements

in the hospital...

For the undernourished geriatric patient admitted to the hospital, Sustagen supplies a therapeutic diet of carefully controlled, essential nutrients to promote good nutrition and hasten convalescence.[1,2] Ideal when tube feeding is necessary,[1] Sustagen is palatable to patients as a beverage.[2]

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During his convalescence at home, the older patient who continues to receive Sustagen is more likely to hold or increase his nutritional gains. Each glassful you specify adds 390 calories to his diet, including 23.5 Gm. protein, 3.5 Gm. fat, and 66.5 Gm. carbohydrate—plus important quantities of all essential vitamins and minerals.

references

(1) Pareira, M. D., *et al.*: J.A.M.A. *156*:810-816 (Oct. 30) 1954.
(2) Winkelstein, A.: Am. J. Gastroenterol. *27*:45-52 (Jan.) 1957.

Mead Johnson Laboratories

Symbol of service in medicine 2558G1

INCREASED LIFE EXPECTANCY FOR HYPERTENSIVES

"Life expectancy seems to be the one criterion that is most reliable and least questioned as a method of evaluating treatment for patients with elevated blood pressure."[1] "It is evident that effective therapy of hypertension will prolong the life of the patient by preventing the dreaded complications of this disease in the brain, the heart and the kidneys." "There is no doubt of the prolongation of life in group 3 and 4 (Keith-Wagener-Barker) by adequate antihypertensive treatment. Some authorities report a 50 per cent, five year survival ratio for treated patients with malignant hypertension as against a 1 per cent survival ratio for untreated patients."[2]

Evaluation based on life expectancy is extremely difficult because of the peril of maintaining an untreated control group.[1] The doctor, however, can evaluate the symptoms related to the elevated blood pressure. . . . We know that retinopathy may improve, the heart may be reduced in size, the electrocardiogram may improve and in favorable cases the blood urea nitrogen level may fall.[2] These are reasonably objective criteria on which to base one's evaluation of treatment.[1]

On the succeeding page is evidence that Unitensen included in any therapeutic regimen may improve the results in hypertension as measured by a regression of objective clinical changes in a substantial proportion of the patients treated.

1. Currens, J. H.: New England J. Med. *261*:1062, 1959.
2. Waldman, S., and Pelner, L.: Am. Pract. & Digest. Treat. *10*:1139, 1959.
3. Cohen, B. M.: paper presented at A.M.A. Convention, June, 1958.
4. Cohen, B. M.: paper presented at Indiana Acad. G. P., March, 1959.
5. Cohen, B. M.: Am. J. Cardiology *1*:748, 1958.
6. Kirkendall, W. J.: J. Iowa M. Soc. *47*:300, 1957.
7. Cherny, W. B., *et al.*: Obst. & Gynec. *9*:515, 1957.
8. Raber, P. A.: Illinois M. J. *108*:171, 1955.
9. McCall, M. L., *et al.*: Obst. & Gynec. *6*:297, 1955.
10. Finnerty, F. A.: Am. J. Med. *17*:629, 1954.

Unlike diuretics or ganglionic blocking agents, Unitensen lowers blood pressure through widespread vasorelaxation. Normal vasomotor responses are not altered, and there is no venous pooling with resulting postural hypotension.[3-5] Through alleviation of cerebral vasospasm, Unitensen promotes cerebral blood flow and oxygen utilization.[6-9] Furthermore, Unitensen increases cardiac efficiency, improves renal function and tends to arrest the progress of vascular damage.[3, 4, 10]

Progress of Objective and Subjective Symptoms in Grades III and IV Hypertension Following Treatment with Unitensen and Unitensen-R

Observations in Patients* Treated up to 2 Years

Observations in Patients* Treated up to 3½ Years

The Course of Subjective Symptoms

Symptom	Number**	Improved	% Improved	Number**	Improved	% Improved
Headache	27	21	77.7	43	38	88.0
Palpitation	20	13	65.0	29	19	65.5
Angina	15	9	60.0	21	16	76.0
Dyspnea	17	8	47.0	27	14	51.0

Objective Changes Following Treatment

Finding	Number**	Improved	% Improved	Number**	Improved	% Improved
Funduscopic Changes	41	24	58.5	59	38	66.0
Enlarged Heart	20	13	65.0	35	23	65.7
Abnormal ECG	37	10	27.0	45	25	55.5
Proteinuria	31	12	38.7	43	27	62.7
Nitrogen Retention	17	6	35.2	28	10	35.7

Left hand charts from Clinical Exhibit "The Ambulatory Patient with Hypertension" presented AMA Convention, San Francisco, June 22-27, 1958, by B. M. Cohen, M.D.

Right hand charts include patients previously reported who had been continuously maintained on Unitensen and Unitensen-R, plus additional patients later added to the study. From Clinical Exhibit "The Office Diagnosis and Treatment of the Patient with Hypertension" presented American Academy of General Practice, Indianapolis, March 18-19, 1959, by B. M. Cohen, M.D.

*All patients in this study were initially classified as Smithwick Grades III and IV.

**Expressed as the number of patients exhibiting the symptom recorded.

UNITENSEN®
Each tablet contains: Cryptenamine (tannates) 2.0 mg.

UNITENSEN-PHEN®
Each tablet contains: Cryptenamine (tannates) 1.0 mg., Phenobarbital 15 mg.

UNITENSEN-R®
Each tablet contains: Cryptenamine (tannates) 1.0 mg., Reserpine 0.1 mg.

UNITENSEN® AQUEOUS
Each cc. contains: 2.0 mg. cryptenamine (acetates) in isotonic saline

new from Neisler
Analexin®
a new class of drug
for the relief of pain and muscle tension

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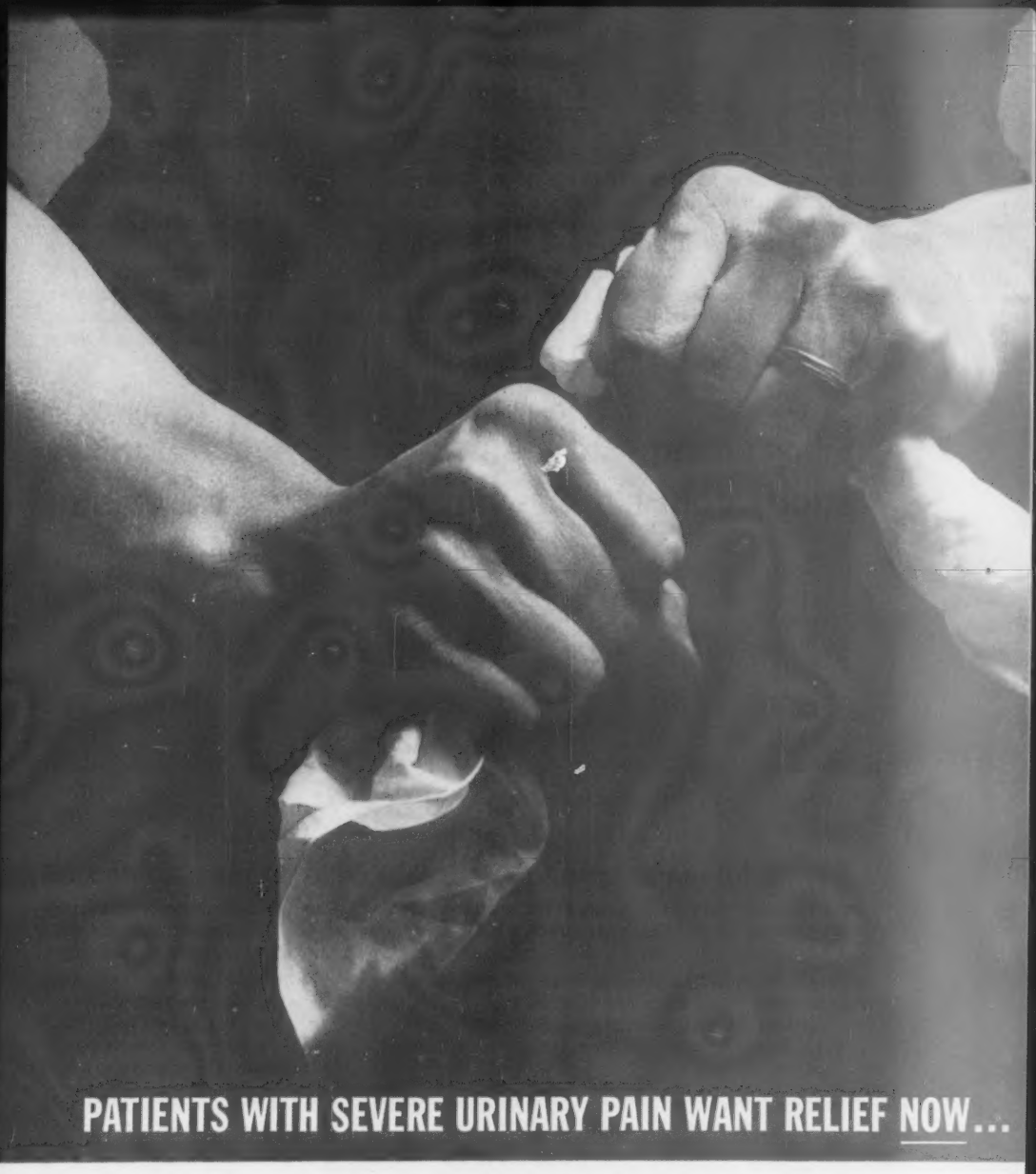
THE PHYSICIAN AND THE CANCER PATIENT

The American Cancer Society is concerned with the *total* cancer problem. A crucial part of this problem relates to the cancer patient and his family. To help the medical profession explore ways and means of meeting the patient's special needs, the scientific session of the Society's next Annual Meeting at the Hotel Biltmore in New York City, October 23-24, 1961, will be devoted to "The Physician and the Total Care of the Cancer Patient." Various specialists will examine the psychological and physical problems facing the cancer patient and his family. Consideration will be given to such topics as decisions in the early care of the cancer patient, counselling the cancer patient, what the patient should be told, care of the advanced cancer patient, society's role in service to the cancer patient.

Through such meetings, the American Cancer Society serves the medical profession by providing a forum for an exchange of information and experience concerning the cancer patient.

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Two Pyridium tablets t.i.d. relieve the pain of urinary infection in only 30 minutes. During the first 3 to 4 days of therapy, Pyridium, prescribed along with any antibacterial of your choice, will make your patient comfortable until the antibacterial reduces inflammation and controls the infection.

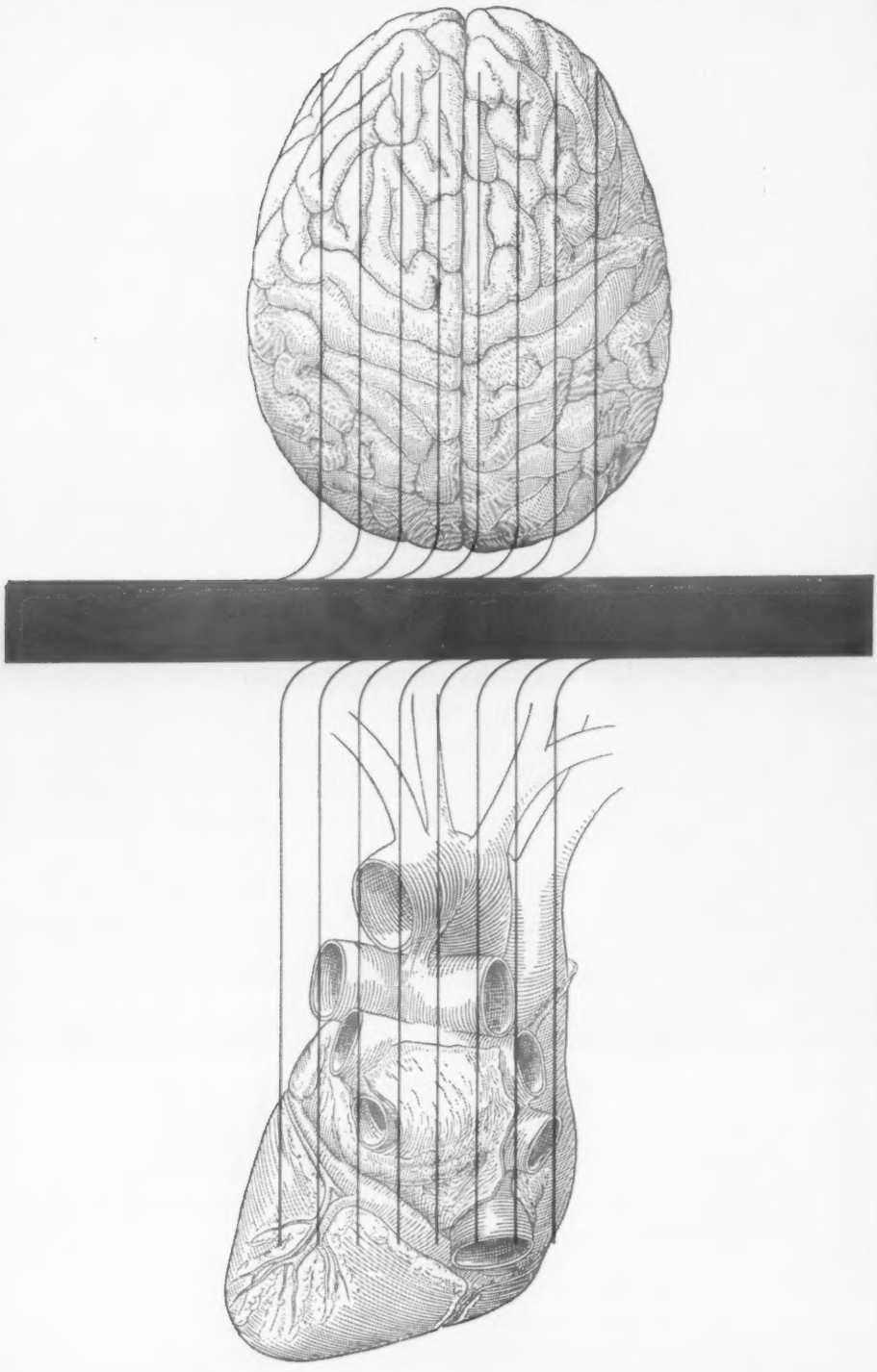
AVERAGE DOSE: Adults—2 tablets t.i.d. Children 9 to 12—1 tablet t.i.d. SUPPLIED: 0.1 Gm. tablets, bottles of 50. PRECAUTIONS: Pyridium is contraindicated in patients with renal insufficiency and/or severe hepatitis. *Full dosage information, available on request, should be consulted before initiating therapy.*

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Makers of TEDRAL GELUSIL PROLOID PERITRATE MANDELAMINE



To lift depression

Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.

Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, *e.g.,* was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.[6]

A single agent, with two distinct primary effects, for two important clinical indications

Marplan

a happy balance of potency/safety

To control pain in "difficult" cases of angina pectoris

Marplan prevents anginal pain,[1-3] increases exercise tolerance[2,4,5] and reduces nitroglycerin requirements.[2,3] It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.

Marplan improves the mental climate: Not only could anginal patients placed on Marplan "... do more than formerly ..."[4] but they also felt better, were more alert, more cheerful.[2,4] The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

Consult literature and dosage instructions, available on request, before prescribing.

Selected bibliography from 38 published papers: **1.** W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. **2.** R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. **3.** N. Bloom, *Virginia M. Month.,* 87:23, 1960. **4.** C. C. Griffith, *Clin. Med.,* 6:1555, 1959. **5.** C. C. Griffith, *Dis. Nerv. System,* 21:(Suppl.), 101, 1960. **6.** L. Alexander and S. R. Lipsett, *Dis. Nerv. System,* 20:(Suppl.), 26, 1959.

MARPLAN® — 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

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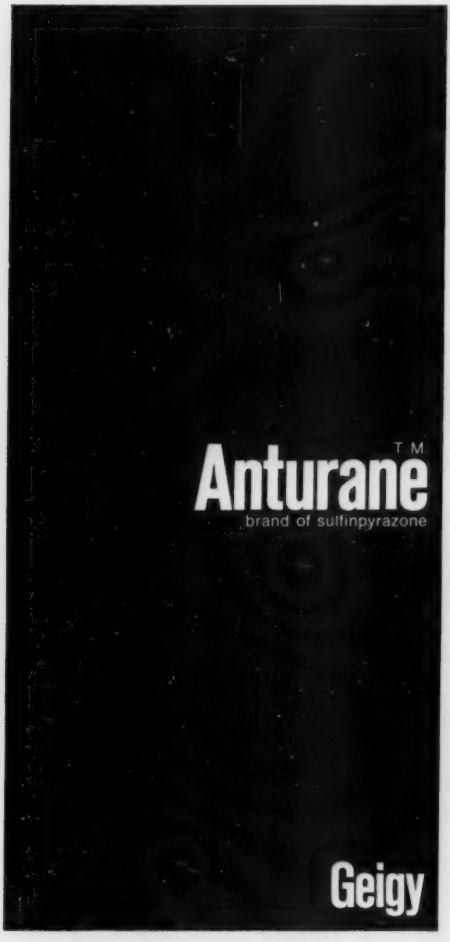
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let your sinusitis, allergy and U.R.I. patients breathe easier!

DIMETAPP Extentabs contain Dimetane®(parabromdylamine [brompheniramine] maleate) 12 mg., phenylephrine HCl 15 mg., and phenylpropanolamine HCl 15 mg., a proved antihistamine and two outstanding decongestants. The dependable Extentab form provides sustained relief from the stuffiness, drip and congestion of sinusitis, colds and U. R. I. for 10-12 hours with a single dose.

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effectively checks the progress of gout by intensive, sustained, uricosuric action

In the long-term treatment of gout, the value of a uricosuric agent such as Anturane in preventing accumulation of the urate deposits responsible for chronic disability and joint derangement is well established.[1]

Clinical experience has demonstrated that Anturane not only prevents formation of new urate deposits, but with sustained therapy, also causes absorption of preexisting tophi.[2] With reduction in hyperuricemia, the incidence and severity of acute attacks are reduced,[3] the mobility of affected joints is improved,[4] and lingering joint pain is relieved.[2,4]

References: 1. Seegmiller, J. E., and Grayzel, A. I.: J.A.M.A. 173:1076, 1960. 2. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. 1:332, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. 17:326, 1958. 4. Gutman, A. B., and Yü, T. F.: Bull. New York Acad. Med. 34:287, 1958.

Full product information regarding dosage, side effects, precautions and contraindications available on request.

Anturane[T.M.], brand of sulfinpyrazone: Scored tablets of 100 mg. in bottles of 100.

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CYTOXAN®

Cyclophosphamide, Mead Johnson

for palliative chemotherapy of certain types of malignant neoplasms

"Cyclophosphamide [Cytoxan] has proved a valuable addition to chemotherapeutic drugs available for the treatment of malignant diseases of the haemopoietic and reticuloendothelial systems.... Particularly effective in Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukaemia, and myelomatosis...."[1]

"Objective data suggest that this agent [Cytoxan] has advantages not possessed by standard alkylating agents now in clinical use."[2]

"With the use of cyclophosphamide [Cytoxan] there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."[3]

Other Advantages in Clinical Practice: Broad-spectrum application. High therapeutic index. No vesicant activity—may be given orally or parenterally.

(1) Matthias, J. Q.; Misiewicz, J. J., and Scott, R. B.: Brit. M. J. 2:1837-1840 (Dec. 24) 1960.
(2) Coggins, P. R.; Ravdin, R. G., and Eisman, S. H.: Cancer *13*:1254-1260 (Nov.-Dec.) 1960.
(3) Papac, R.; Petrakis, N. L.; Amini, F., and Wood, D. A.: J.A.M.A. *172*:1387-1391 (March 26) 1960.

DOSAGE: *For neoplasms relatively susceptible to Cytoxan* — Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2-3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan — Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage — The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2-3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.



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Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the Fe^{59} isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

erythropoietin levels—new criteria in diagnosis of anemia—Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

can medication increase erythropoietin levels? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF, the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Physiol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

For a complete background file on erythropoietin, please write to the Medical Service Department of:

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a pair of gynecologic patients:



both are free of pain—but only one is on

DILAUDID®

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swift, sure analgesia normally unmarred by nausea and vomiting

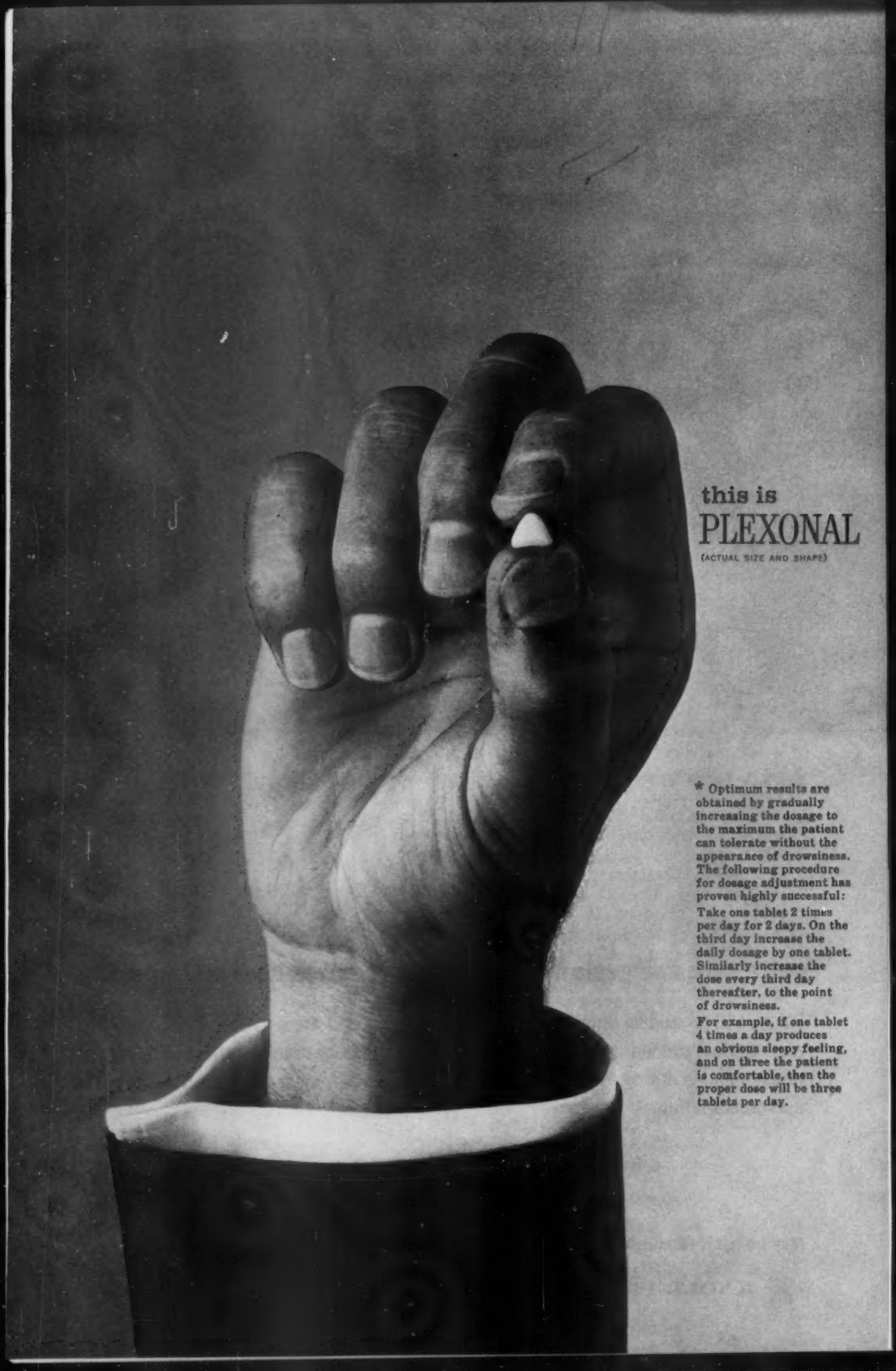
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Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

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In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."[2]

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

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Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day.*

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1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.

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1. Biegeleisen, H. I.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.



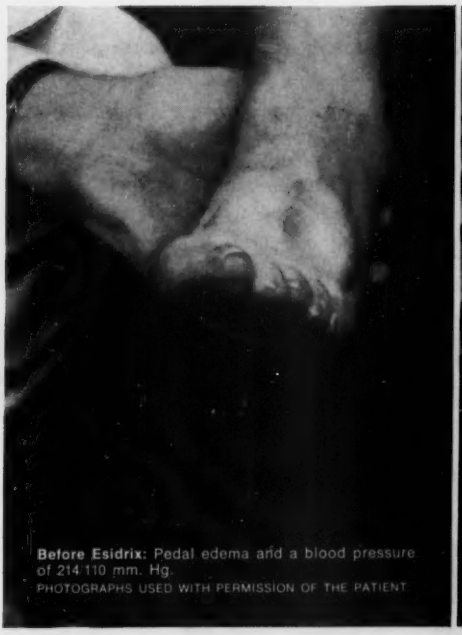
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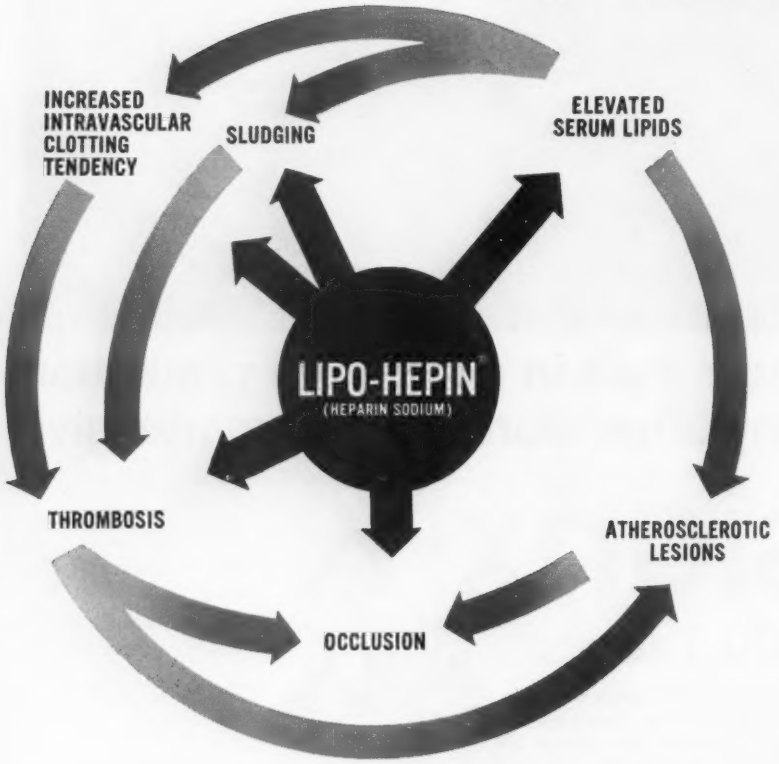
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References: 1. Altschule, M. D.: M. Sc. *6*:560, 1959. 2. Rubin, J. M.; Baylin, G. J.; Legerton, C. W., and Texter, E. C., Jr.: Gastroenterology *23*:252, 1953. 3. Texter, E. C., *et al.*: Ann. Int. Med. *51*:1275, 1959. 4. Kasich, A. M.; Boleman, A. P., Jr., and Rafsky, J. C.: Am. J. Digest. Dis. *1*:361, 1956. 5. Roth, J. L. A.; Wechsler, R. L., and Bockus, H. L.: Gastroenterology *31*:993, 1956. 6. Rafsky, J. D.: Gastroenterology *27*:29, 1954.

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Bedell, W.C.: J.A.M.A. **173**:1811, August 20, 1960.

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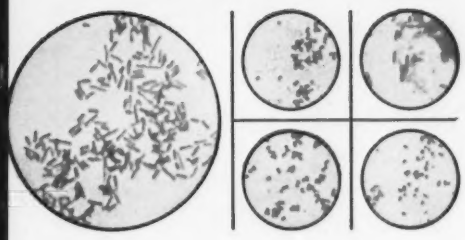
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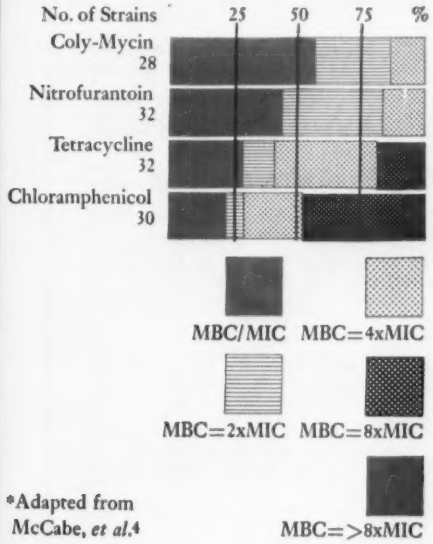
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References: 1. Seneca, H.; Lattimer, J. K., and Zinsser, H. H.: New York J. Med. *60*:3630, 1960. 2. Roberts, C. E., Jr., and Kirby, W. M. M.: Colistin in the treatment of hospitalized patients with Pseudomonas infection. Presented at the 1960 Conference on Anti-Microbial Agents, Washington, D. C. 3. Stamey, T. A., in Conn, H. F. (Ed.): Current Therapy 1961, Philadelphia, W. B. Saunders Company, 1961, p. 357. 4. McCabe, W. R.; Jackson, G. G., and Kozij, V. M.: Antibiotics Annual 1959-1960, New York, Antibiotica, Inc., 1960, p. 80.

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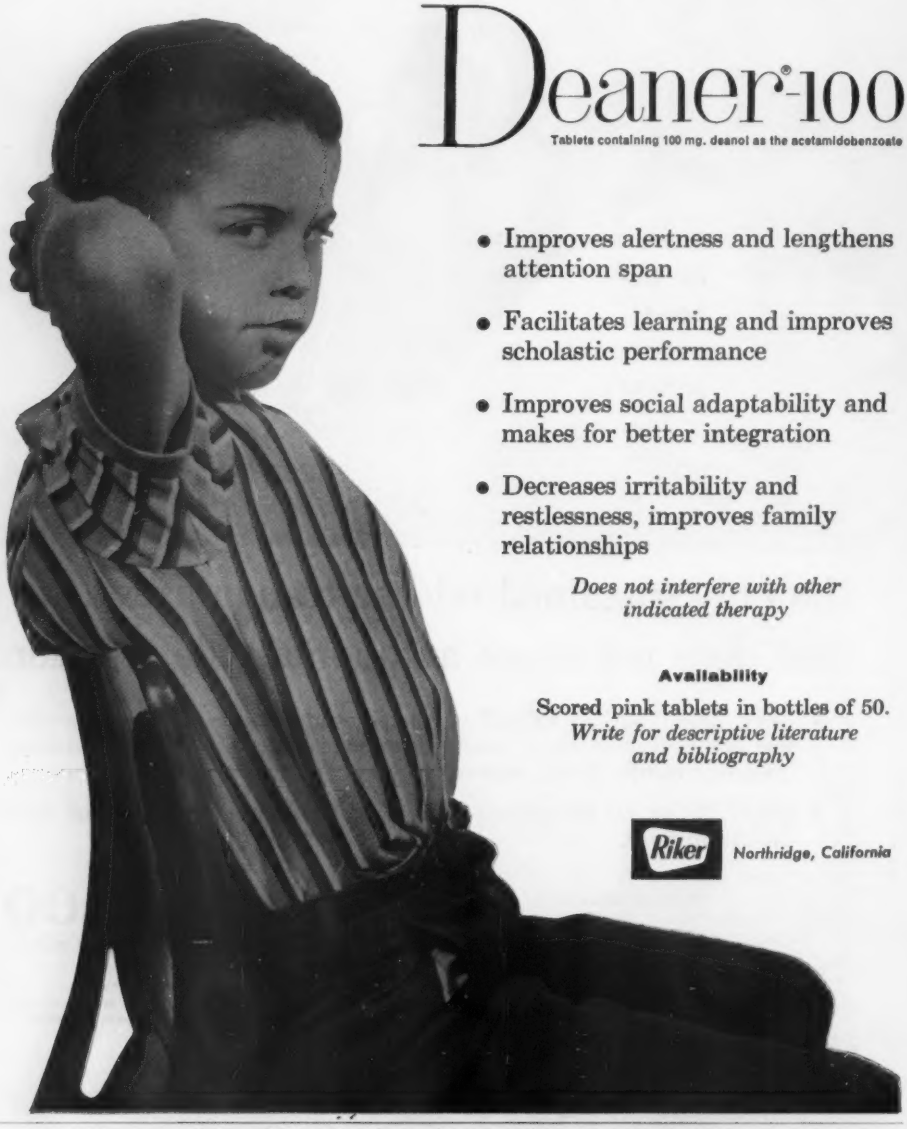
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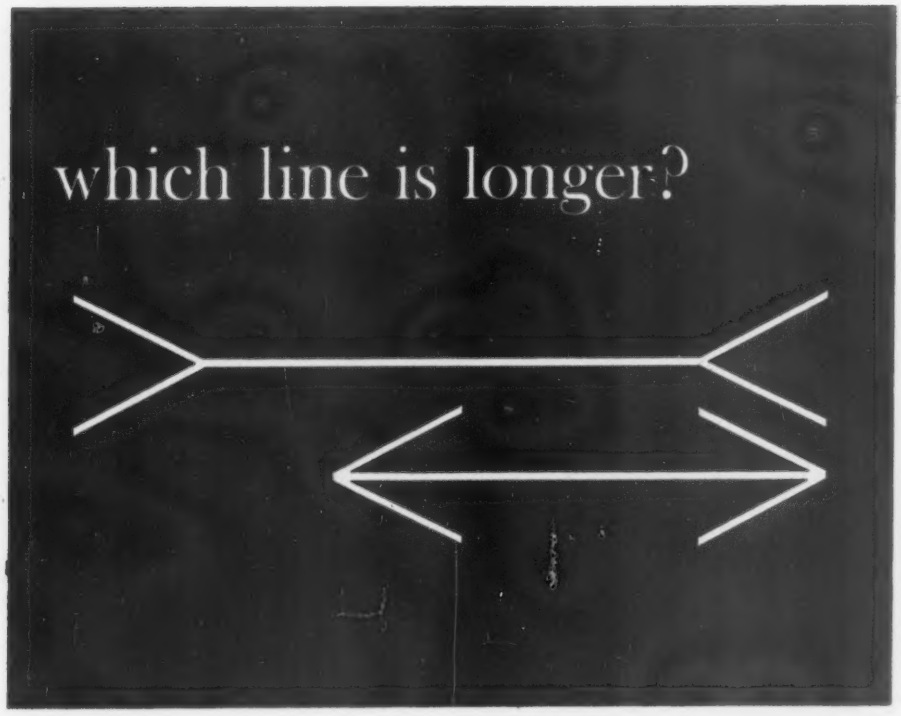
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1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:129, 1960.

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